Current and future perspectives for wastewater-based epidemiology as a monitoring tool for pharmaceutical use

Current and future perspectives for wastewater-based epidemiology as a monitoring tool for pharmaceutical use

Boogaerts Tim[a,*], Ahmed Fahad[b], Choi Phil.M.[b,c], Tscharke Benjamin[b], O' Brien Jake[b], De Loof Hans[d], Gao Jianfa[e], Thai Phong[b], Thomas Kevin[b], Mueller Jochen F.[b], Hall Wayne[b,f], Covaci Adrian[a], & van Nuijs Alexander L.N.[a,*]

[a] *Toxicological Centre, University of Antwerp, Belgium, Universiteitsplein 1, 2610 Antwerp, Belgium*

[b] *Queensland Alliance for Environmental Health Sciences (QAEHS), University of Queensland, 20 Cornwall St, Woolloongabba QLD 4102, Australia*

[c] *Water Unit, Health Protection Branch, Prevention Division, Queensland Health, GPO Box 48 Brisbane QLD 4001, Australia*

[d] *Laboratory of Physiopharmacology, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium*

[e] *College of Chemistry and Environmental Engineering, Shenzhen University, 1066 Xueyuan Avenue, Shenzhen, 518060, China*

[f] *Centre for Youth Substance Abuse, University of Queensland, 17 Upland Road, Woolloongabba QLD 4102, Australia*

(*): corresponding author

Email: Tim.boogaerts@uantwerpen.be; alexander.vannuijs@uantwerpen.be

Key words

- Wastewater-based epidemiology
- Drug Utilization Research
- Pharmacoepidemiology
- Pharmaceutical (mis)use

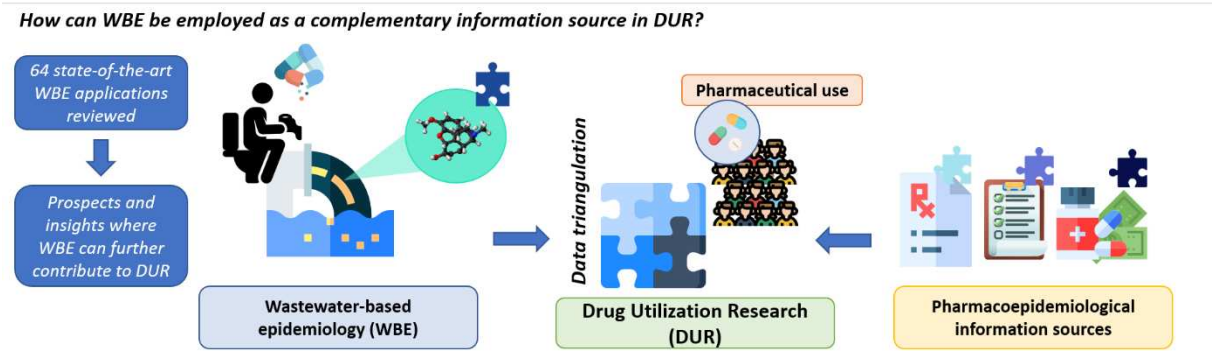
Abstract

The medical and societal consequences of the misuse of pharmaceuticals clearly justifies the need for comprehensive drug utilization research (DUR). Wastewater-based epidemiology (WBE) employs the analysis of human metabolic excretion products in wastewater to monitor consumption patterns of xenobiotics at the population level. Recently, WBE has demonstrated its potential to evaluate lifestyle factors such as illicit drug, alcohol and tobacco consumption at the population level, in near real-time and with high spatial and temporal resolution. Up until now there have been fewer WBE studies investigating health biomarkers such as pharmaceuticals.

WBE publications monitoring the consumption of pharmaceuticals were systematically reviewed from three databases (PubMed, Web of Science and Google Scholar). 64 publications that reported population-normalised loads or defined daily doses of pharmaceuticals were selected.

We document that WBE could be employed as a complementary information source for DUR. Interest in using WBE approaches for monitoring pharmaceutical use is growing but more foundation research (e.g. compound-specific uncertainties) is required to link WBE data to routine pharmacoepidemiologic information sources and workflows. WBE offers the possiblity of i) estimating consumption of pharmaceuticals through the analysis of human metabolic excretion products in wastewater; ii) monitoring spatial and temporal comsumption patterns of pharmaceuticals continuously and in near real-time; and iii) triangulating data with other DUR information sources to assess the impacts of strategies or interventions to reduce inappropriate use of pharmaceuticals.

Graphical abstract



1. Introduction

The development of new and more effective pharmaceuticals in the last decades has contributed to a significant decrease in mortality, an improved quality of life for people with chronic illnesses and reduced time in hospital (Lichtenberg, 2014; Poluzzi et al., 2016). Nevertheless, misuse and abuse of pharmaceuticals can also have negative consequences, such as increased emergency room visits, treatment admissions for prescription drug use disorders and overdose deaths (National Institute of Drug Abuse, 2018; Poluzzi et al., 2016). In addition, 20% of health spending is wasteful and can be reduced by preventing the misuse and mis- and overprescription of pharmaceuticals (Organisation for Economic Co-operation and Development, 2018). The medical consequences and economic burden of the inappropriate use of pharmaceuticals has encouraged comprehensive drug utilization research (DUR) over the past decades (Poluzzi et al., 2016). Currently, DUR relies on data from the sales, billing, prescription and movement through the distribution chain of pharmaceuticals. All of this information is necessary to ensure the availability of safe, high-quality and efficacious treatments (World Health Organization, 2003). These information sources can be used to establish utilization patterns for specific pharmaceuticals and may provide a proxy for the prevalence of the diseases treated by these drugs (Chen & Briesacher, 2011; World Health Organization, 2003). Definitions for DUR terminology can be found in Table S1.

Data on the illegal trade or clandestine manufacturing of pharmaceuticals are not covered by traditional DUR figures (Diamanti et al., 2019; European Monitoring Centre for Drugs and Drug Addiction, 2019b), which can lead to an underestimation of pharmaceutical consumption (van Nuijs et al., 2015). In some health care systems, incomplete coverage of these data sources might lead to gaps between the number of prescriptions and overall drug utilisation (i.e. scripts may not be filled, filled scripts may not be consumed, and pharmaceuticals may not be taken in the recommended doses or by the person for whom they were prescribed). Additionally, the locality where a prescription is filled may differ from where consumption occurs. Some patients may not be able to afford to fill their prescriptions, particularly when it comes to repeat prescriptions or due to associated costs or unwanted side effects. These data also do not always include information on the amounts of pharmaceuticals used in hospitals and so may only record the use of reimbursed pharmaceuticals. (Poluzzi et al., 2016; World Health Organization, 2003). Furthermore, a limitation of currently used methods for drug utilisation data is the lack of spatial specificity, the lag in data acquisition and the infrequency of data reporting (e.g. this is often only be done on a yearly basis). The resolution of the data is also dependent on the quality of the health care system and may differ between jurisdictions within the same country.

In order to provide community-health information on exposure to xenobiotics, wastewater-based epidemiology (WBE) measures biomarker concentrations in untreated wastewater and converts these to per capita mass load estimates using daily wastewater flow rates and population number in the catchment area (Fig. 1) (Boogaerts, Covaci, Kinyua, Neels, & van Nuijs, 2016; P. Choi et al., 2018; Daughton, 2018; Lai et al., 2013; van Wel et al., 2016; Zuccato, Chiabrando, Castiglioni, Bagnati, & Fanelli, 2008). Target analytes can be quantified at trace levels (ng/L) by applying specific, accurate and precise bioanalytical methods such as solid phase extraction and liquid chromatography mass spectrometry (LC-MS/MS) (Andrés-Costa, Andreu, & Picó, 2017; Baker & Kasprzyk-Hordern, 2011a; Botero-Coy et al., 2018; Fatta, Achilleos, Nikolaou, & Meriç, 2007). Although WBE is a relatively new scientific discipline, it has rapidly realised its potential to provide independent, timely, low cost/resource and complementary epidemiologic information on the exposure to and consumption of xenobiotics at high spatial and temporal resolutions (Banta-Green et al., 2009; Huerta-Fontela, Galceran, Martin-Alonso, & Ventura, 2008; Karolak, Nefau, Bailly, Solgadi, & Levi, 2010; Kasprzyk-Hordern, Dinsdale, & Guwy, 2009; Mari et al., 2009; Metcalfe, Tindale, Li, Rodayan, & Yargeau, 2010; Postigo, López de Alda, & Barceló, 2010; Terzic, Senta, & Ahel, 2010; van Nuijs et al., 2009; Zuccato et al., 2005). This is reflected in the increasing numbers of publications in this field (Fig. S1) (P. Choi et al., 2018). The majority of WBE research has focussed on back-estimating illicit drug consumption and only a few have investigated the use of pharmaceuticals (P. Choi et al., 2018; Gracia-Lor et al., 2017). In addition, most of the WBE applications on pharmaceuticals i) have used these data to estimate population size (P. Choi et al., 2018; Lai et al., 2011); ii) to evaluate the illegal use of specific pharmaceuticals (P. Choi et al., 2018; Thai, Lai, Edirisinghe, et al., 2016) or iii) to associate pharmaceutical loads with environmental stressors (P. Choi et al., 2018; Phung et al., 2017).

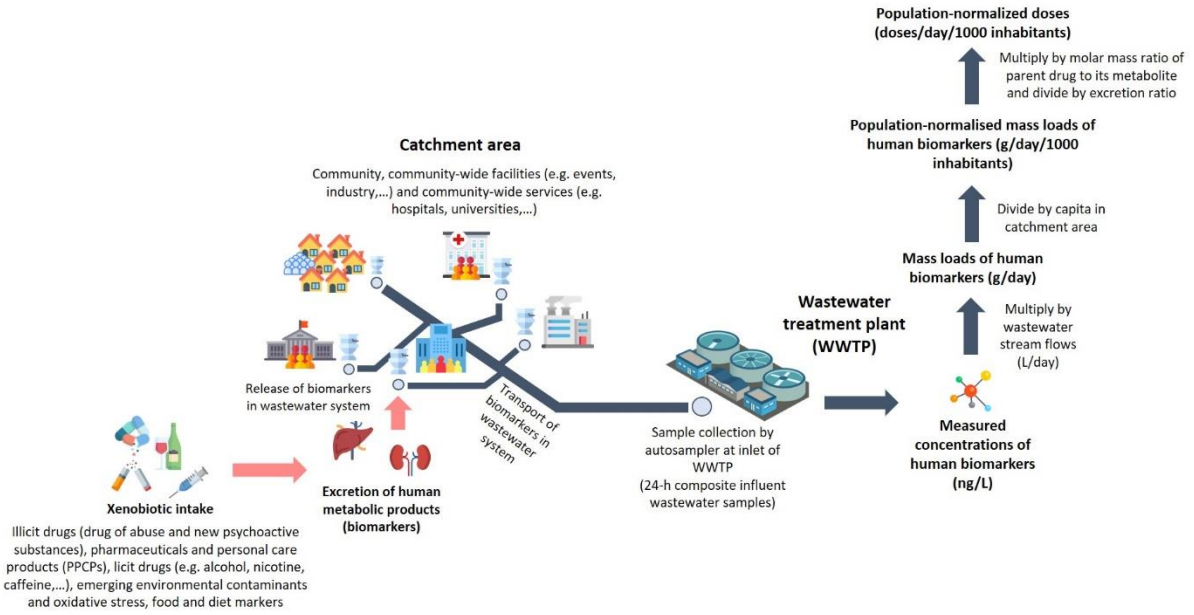


Fig. 1 Schematic overview of WBE for determining pharmaceutical consumption. *Adapted from Choi et al* (P. Choi et al., 2018).

Importantly, WBE cannot provide any information on the charactersistics of of the user and his personal consumption. That is, it cannot tell us about: the administration form, co-consumption, dose purity, dose frequency, individual compliance, drug use preferences, or the socio-demographic characteristics of individual patients. Nor can diversion and changes within the drug-using cohort be quantified by WBE. Specifically, if an increase was observed WBE cannot distinguish between the following possibilities i) more individuals are consuming at the same rate, ii) slightly more individuals consuming and at a higher rate each, iii) the same number of individuals consuming a higher total amount each, or iv) one group of individuals in the cohort consuming more than another group. Nevertheless, wastewater samples can be analyzed retrospectively to provide aggregated consumption estimates (Boogaerts et al., 2016; Burgard et al., 2019; Mackie et al., 2019) with easily adjusted spatio-temporal frequencies and short time-lags in gathering and reporting data. While specific socio-demographic features of individuals might not easily be obtained, WBE can provide a spatial comparison between different populations with different socio-economic status at a community level (P. Choi et al., 2019).

We review the current situation of applying WBE towards understanding pharmaceutical consumption and provide an overview of analytical information and biomarkers used to monitor pharmaceutical use in defined population groups. Our aim is to document state-of-the art WBE applications on pharmaceutical consumption to give a better understanding on the future research that is needed to move forward WBE as a complementary epidemiological

information source in DUR. In this lights, this review aims to provide key insights and prospects where WBE can further contribute to DUR.

2. Literature search and eligibility criteria

Multiple literature searches were conducted (between July 2020 and March 2021) to identify all publications (i.e. research papers, short reports, letters,…) on WBE investigations of pharmaceutical consumption. PubMed, Web of Science and Google Scholar were queried as illustrated in Table 1. Since WBE was first applied in 2008, we only searched for publications between 2008 and March 2021. An updated search was performed on a monthly basis to identify new emerging WBE applications on pharmaceuticals.

Table 1 Applied search combinations during the advanced literature search

Specified search terms	**Search records**
(sewage OR wastewater OR "wastewater epidemiology") AND (pharmaceuticals OR medicines)	6498
((wastewater OR sewage OR "wastewater based epidemiology") AND ("pharmaceuticals" OR "medicines")) AND consum*	350
(((((wastewater) OR sewage) AND influent) AND pharmaceuticals) NOT "removal efficien*") NOT sludge	165
((((("wastewater epidemiology") OR "sewage epidemiology") OR "wastewater based epidemiology") AND pharmaceuticals) AND consum*	71
(sewage OR wastewater OR "wastewater epidemiology") AND pharmaceutical AND "influent wastewater"	45
((("wastewater based epidemiology") AND (pharmaceutical OR medicines)) AND (consumption OR "population normalised"))	28
("wastewater epidemiology"[Title/Abstract] OR sewage [Title/Abstract] OR wastewater[Title/Abstract]) AND (pharmaceuticals OR medicines) AND "population health"	26
wastewater AND influent AND pharmaceutical AND loads NOT effluent	16

Table 1 describes the different keyword combinations that were applied to identify eligible studies for this review. After a preliminary screening against the eligibility criteria, 122 publications were selected from this wide range of search records. This initial search was further screened against the strict inclusion criteria defined below. This final screening resulted in 64 publications qualified for full text review. While the total number of WBE applications on pharmaceuticals is relatively small, interest in this field of research has grown for the last six years (~ 9 papers per year on average), as illustrated in Fig S1. Numerous other studies report concentrations of pharmaceuticals in influent wastewater (IWW) (Baker & Kasprzyk-Hordern, 2011b; Bodik, Mackulak, Faberova, & Ivanova, 2016). However, in WBE, concentrations are not suitable to estimate community-wide use of pharmaceuticals because of fluctuations in flow rates and population sizes. For this reason, it is imperative to normalize measured concentrations for varying population sizes and flow rates to allow reliable comparisons between locations. Additionally, these descriptive studies did not triangulate with other data of tested specific

hypothesis about the spatio-temporal patterns of use. Therefore, these studies were not included in this review. By normalizing to population sizes and flow rates, WBE offers the possibility to compare intra- and intercountry normalized-loads of pharmaceuticals (Ahmed et al., 2020; Bodik et al., 2016; Pereira, Silva, Meisel, Lino, & Pena, 2015). For these reasons, the selection of eligible cases goes beyond simply reporting of pharmaceutical concentrations in IWW.

We included (i) WBE studies that estimated population-normalised mass loads of excreted human metabolic pharmaceutical biomarkers (mg/day/1000 inhabitants) and (ii) WBE studies in which pharmaceutical doses were back-calculated using measured concentrations of the biomarkers (doses/day/inhabitant). For this purpose, we excluded wastewater studies on pharmaceuticals that focused exclusively on (i) method development and validation; (ii) evaluating removal efficiencies during wastewater treatment; (iii) investigating pharmaceuticals as a potential source of contamination in aquatic environments and (iv) evaluating the use pharmaceutical concentrations as population size markers. Citation tracking and searches in author's bibliographies were performed to track down additional references. Detailed information on the applied analytical techniques and current WBE biomarkers is given elsewhere (Baker & Kasprzyk-Hordern, 2011a; P. Choi et al., 2018; Gracia-Lor et al., 2017; van Nuijs et al., 2011).

3. WBE applications on pharmaceuticals: state-of-the-art applications

The final selection of 64 WBE applications can be categorized in different types including spatial and temporal comparisons, triangulating with sales and/or prescription statistics, monitoring pharmaceuticals as proxies of disease, correlations with socio-demographics, and evaluating illicit use of pharmaceuiticals (Fig. 2). Table S2 summarizes all currently available WBE applications on pharmaceuticals. In this section, we will focus on the most prevalent applications.

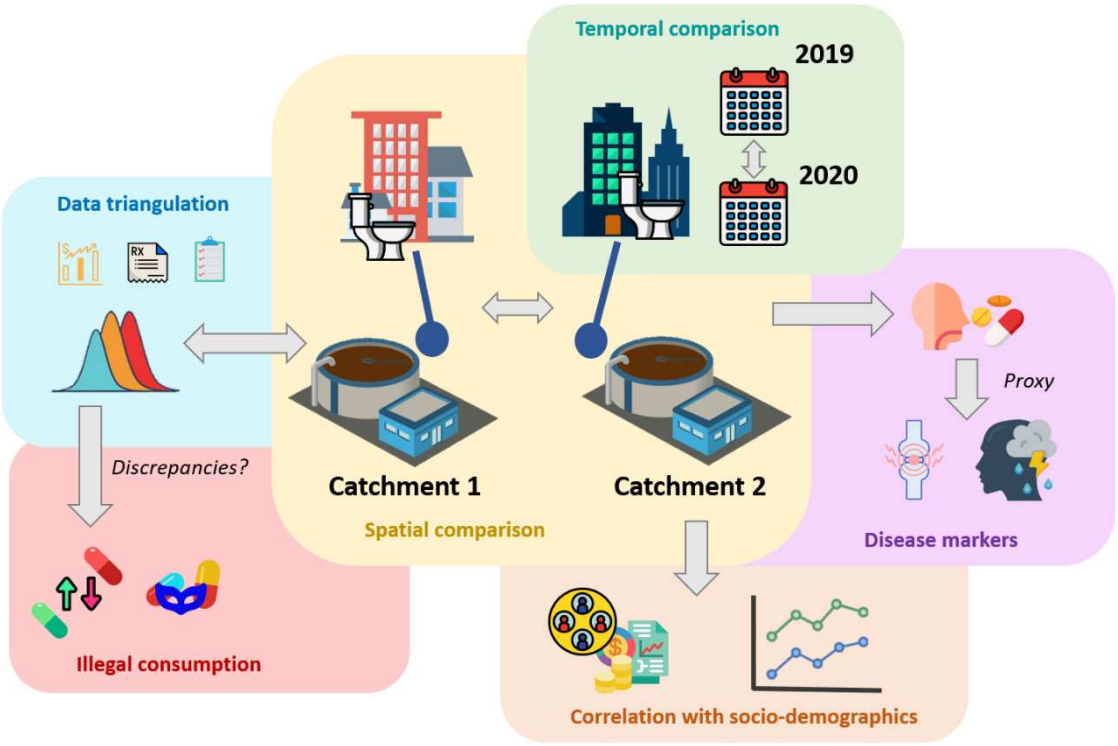


Fig. 2 Overview of all current WBE applications on pharmaceuticals

3.1. Spatio-temporal analysis of pharmaceutical consumption

Population-normalized biomarker mass loads can be employed as a proxy for consumption of the parent compound. This normalization enables the comparison of consumption patterns across different locations and different time points. This proxy is more appropriate compared to per capita doses per day since less uncertainty is associated with the back-calculations (i.e. large uncertainties associated with excretion factors).

3.1.1. Spatial comparisons of pharmaceutical use

45 out of the 64 studies demonstrate the ability of WBE to investigate spatial differences in the consumption of pharmaceuticals (Ahmed et al., 2020; Australian Crime Intelligence Commision, 2020; Bade, Ghetia, White, & Gerber, 2020; Baker, Ocenaskova, Kvicalova, & Kasprzyk-Hordern, 2012; Baz-Lomba et al., 2016; Bodik et al., 2016; Boogaerts, Degreef, Covaci, & van Nuijs, 2019; Boogaerts, Quireyns, Covaci, De Loof, & van Nuijs, 2021; Burgard, Fuller, Becker, Ferrell, & Dinglasan-Panlilio, 2013; Castrignano et al., 2020; Causanilles, Emke, & de Voogt, 2016; Causanilles et al., 2018, 2017; P. M. Choi et al., 2018; P. Choi et al., 2019; Croft, Huffines, Pathak, & Subedi, 2020; Duan, Meng, Wen, & Chen, 2013; Escolà Casas et al., 2021; Fáberová, Bodík, Ivanová, Grabic, & Mackuľak, 2017; Fallati et al., 2020; Gao et al., 2016; Gomez-Canela, Sala-Comorera, Pueyo, Barata, & Lacorte, 2019; Gushgari, Driver, Steele, & Halden, 2018; Kim & Oh, 2020; Krizman, Senta, Ahel, & Terzic, 2016;

Mackulak et al., 2016, 2019; Mirzaei, Mesdaghinia, Hoseini, & Yunesian, 2019; Ort, Lawrence, Reungoat, Eaglesham, et al., 2010; Ostman, Fick, Nasstrom, & Lindberg, 2014; Pereira et al., 2015; Riva, Castiglioni, Pacciani, & Zuccato, 2020; Shao et al., 2021; Skees, Foppe, Loganathan, & Subedi, 2018; Subedi, Balakrishna, Joshua, & Kannan, 2017; Subedi & Kannan, 2015; Thiebault, Fougere, Destandau, Rety, & Jacob, 2017; Thomaidis et al., 2016; Venhuis, de Voogt, Emke, Causanilles, & Keizers, 2014; Xiao et al., 2019; J.-H. Yan et al., 2019; Q. Yan et al., 2014; Yargeau, Taylor, Li, Rodayan, & Metcalfe, 2014; Zhang et al., 2019, 2018). 34 studies indicate that WBE is sensitive enough to detect spatial variations in pharmaceutical use within countries (town/village level) and, therefore, able to identify locations that differ in pharmaceutical use. While some traditional DUR information sources may lack geospatial granulity, WBE can monitor consumption patterns at the scale of suburbs and regions within a metropolitan area. In contrast to the studies that focus on differences in pharmaceutical use within a specific country, only 8 studies provide a between-country spatial comparison (Baz-Lomba et al., 2016; Castrignano et al., 2020; Causanilles et al., 2018; Duan et al., 2013; Fallati et al., 2020; Gao et al., 2016; Subedi et al., 2017; Q. Yan et al., 2014). With traditional DUR information sources, it can be difficult to compare pharmaceutical consumption between jurisdictions when organization of the health care systems and therefore also data collection are completely different. In this light, Fallati et al. investigated the consumption of a broad range of pharmaceuticals in different therapeutic classes with WBE in Malé compared to Milan and Oslo (Fallati et al., 2020). Consumption in Malé could therefore be estimed through WBE as local prescription data were not available.

An under-explored area is the use of WBE within sub-catchments such as hospitals or university campuses, suburbs, or aged care facilities. Limited studies show the potential for WBE to monitor the consumption of pharmaceuticals in subsets of the population and during specific events (Burgard et al., 2019; Gomez-Canela et al., 2019; Gul, Gul, Stamper, Godfrey, & ElSohly, 2018; Gul, Stamper, Godfrey, Gul, & ElSohly, 2016; Gushgari et al., 2018; Kosma, Nannou, Boti, & Albanis, 2019; Mackulak et al., 2016; Ort, Lawrence, Reungoat, Eaglesham, et al., 2010; Stamper, Gul, Godfrey, Gul, & ElSohly, 2016; van Dyken et al., 2016). In this light, three WBE studies focused on the consumption of opioids and benzodiazepines during football games at the Mississippi University campus (Gul et al., 2018, 2016; Stamper et al., 2016) and found substantial increases in tramadol and hydrocodone while concentrations in the municipal IWW samples were unchanged.

3.1.2. Temporal analysis of pharmaceutical consumption

Due to its high temporal resolution, WBE can be employed to obtain useful information on the consumption patterns of pharmaceuticals over time. For instance, long-term trends can indicate whether pharmaceutical use is

stable, fluctuating, declining or on the rise. Additionally, seasonal patterns can highlight temporal changes with a fixed frequency (e.g. between months of the year, between same months in different years). Furthermore, within-week trends can reveal recreational pharmaceutical use versus habitual consumption (Tscharke, Chen, Gerber, & White, 2016).

3.1.2.1 Within-week trends in pharmaceutical loads

To date, because sampling and analysis costs are typically relatively low, most studies have conducted 24-hour composite sampling for multiple days. This allows for a temporal resolution that is difficult to obtain using other methods. Differences in the mass loads measured on a daily basis can point to the recreational use of pharmaceuticals on, for example, weekends as many pharmaceuticals, such as antihypertensives and antidepressants, have low interdaily variability (Ahmed et al., 2020; Australian Crime Intelligence Commision, 2020; Been et al., 2015; Causanilles et al., 2016; Mastroianni, Lopez-Garcia, Postigo, Barcelo, & Lopez de Alda, 2017; Tscharke, Chen, Gerber, & White, 2015). Studies have thus found weekend differences in per capita normalized mass loads for i) tramadol, methadone and possibly amitriptyline in the Czech Republic (Baker et al., 2012), ii) tramadol, codeine and oxazepam in Slovakia (Mackulak et al., 2016) and iii) tramadol, diclofenac (NSAID), methadone and antibiotics (sulfamethoxazole and trimethoprim) in France (Thiebault et al., 2017). Due to the high frequency, analyses can also identify correlations between trends in the consumption of pharmaceuticals that may be of concern.

Interestingly, two out of four studies estimating population-normalized mass loads of sildenafil found no difference between weekend and weekday in the Netherlands and in 8 European cities (Causanilles et al., 2016, 2018), wheras two studies, in England and in the Czech Republic, that document such a difference (Baker, Barron, & Kasprzyk-Hordern, 2014; Baker et al., 2012). Similarly, the ADHD medication methylphendidate, having possible stimulant effects, showed increased use on weekends in some European cities (Baz-Lomba et al., 2016) while this effect was not found on a university campus (Gushgari et al., 2018).

3.1.2.2 Seasonality and long-term temporal trends

Most of the studies included in this review focused on a period of 7 days or less and fewer than 10 pharmaceuticals for only one or two WWTPs, as indicated in Table S2. About half of the publications that assessed pharmaceutical population-normalised mass loads in wastewater sampled more than 7 days and reported long-term temporal data (i.e. trends that occur over several months or years). The most investigated substances were opioids, antibiotics, benzodiazepines and antidepressants. In contrast to illicit drugs, short-term variations in pharmaceutical

consumption are less expected since pharmaceutical treatment requires frequent dose intervals and fixed treatment schemes. For this reason, it is more interesting to monitor long-term consumption patterns in the use of pharmaceuticals.

Higher mass loads were found in the winter for antidepressants, antibiotics (Golovko, Kumar, Fedorova, Randak, & Grabic, 2014), tramadol and venlafaxine (Mackulak et al., 2016) while summer and autumn recorded higher mass loads of NSAIDs (Papageorgiou, Kosma, & Lambropoulou, 2016), antihistamines, lipid regulators (Golovko et al., 2014), codeine and oxazepam (Mackulak et al., 2016). For carbamazepine, oxazepam, methadone, citalopram, metformine and memantine, population-normalized mass loads were relatively consistent between seasons (Golovko et al., 2014; Mackulak et al., 2016; Xiao et al., 2019).

Pereira et al and Krizman et al (Krizman et al., 2016; Pereira et al., 2015) also highlighted that seasonal differences in consumption estimates may be due to tourism, as higher use of some pharmaceuticals was observed during summer periods at coastal tourist destinations, when compared with equivalent non-tourist destinations (Pereira et al., 2015). This seasonal effect was addressed in Phung et al. by directly investigating the link between temperature and consumption of a handful of pharmaceuticals (Phung et al., 2017). They found increased temperature associated with increased naproxen (NSAID) loads, while decreased temperature related to increasing atenolol consumption. No significant changes with temperature were observed for caffeine, codeine, carbamazepine and hydrochlorothiazide. The changes in consumption measured in that study could also be due to changing population demographics throughout the year, e.g. an efflux of older people during summer, making it more difficult to compare studies with multiple years of data from multiple locations. However, these studies may highlight seasonal effects on consumption of substances; changes that may be geographically or culturally specific.

Of the few long term studies available on pharmaceutical consumption key findings include a decreasing trends in methadone consumption and an increase in oxycodone and fentanyl in Adelaide between 2011 and 2015 (Tscharke et al., 2016). Sildenafil and metformin use increased in the Netherlands (Causanilles et al., 2016) and China (Xiao et al., 2019) respectively over more than 3 years. Notably, consistent use patterns of methadone, morphine and codeine were observed over time in Lausanne, Zagreb and Adelaide, respectively (Been et al., 2015; Krizman-Matasic, Senta, Kostanjevecki, Ahel, & Terzic, 2019; Tscharke et al., 2016).

3.2. WBE biomarkers for disease and disease outbreaks

The WBE approach demonstrates that urinary human biomarkers identified and quantified in wastewater can provide a perspective on a population's health in (near)-real time (Daughton, 2018). Specific pharmaceuticals or

a combination of pharmaceuticals are generally prescribed to treat diseases (Thomas & Reid, 2011). Several WBE studies demonstrate the potential for WBE biomarkers to serve as a proxy measure for treated disease prevalence. By measuring at high spatio-temporal resolution, it will be possible to monitor the evolution of different diseases in specific locations and make area-specific assessments about their burden and monitor in near-real-time the evolution of specific diseases.

This can however be complicated by a number of factors such as underdiagnosis or undertreatment. Additionally, some diseases need a combination treatment while some pharmaceuticals are used to treat multiple diseases. Uncertainties as arise for some diseases (e.g. depressive disorders), where non-pharmacological treatment might be prioritized over pharmaceutical treatment. Furthermore a lack of compliance or recreational use should also be taken into account. Therefore, it is imperative to proceed with caution when using WBE as a proxy for specific disease prevalence.

To date, four Chinese WBE studies have used metformin as a proxy for type 2 diabetes (Shao et al., 2021; Song et al., 2020; Xiao et al., 2019; J.-H. Yan et al., 2019). While they successfully captured metformin consumption in Chinese communities, measurement of other antidiabetic drugs (e.g. sulfonylureas) would be necessary for a more comprehensive picture on the prevalence of this disease. Insulin has been a key component of management in patients with type 2 diabetes mellitus (T2DM), who require insulin therapy to maintain normal hemoglobin A1c (HbA1c) levels (Scheurer, Brauch, & Lange, 2009). While most diabetic drugs are excreted in sufficient amounts in urine (Gong, Goswami, Giacomini, Altman, & Klein, 2012; SHELDON, ANDERSON, & STONER, 1965), almost all insulin is reabsorbed in the kidney with only trace amounts found in urine (Hanefeld, 2014). Therefore, the use of WBE as a proxy for type 2 diabetes is not viable in the absence of suitable biomarkers for insulin and additional biomarkers for antidiabetic drugs.

Ahmed et al. measured oxypurinol as a disease biomarker in wastewater to estimate the prevalence of treated gout in Australia (Ahmed et al., 2020). Gout prevalence was estimated to be 2.7% in this study, which was comparable to estimates from other epidemiologic studies (Proudman et al., 2019; Robinson, Kempe, Tebbutt, & Roberts, 2017). However, while defined daily doses (DDD) provided a good basis for comparing the consumption of pharmaceuticals between different countries, it might be more challenging to use it to estimate the prevalence of disease because of variations in doses prescribed per patient. Additionally, compliance is also universally low in these patient groups which increases the uncertainty in these estimates (Silva et al., 2010).

290 Antibiotics have significantly reduced morbidity and mortality from many infectious diseases (Bérdy, 2012). Their
291 total global consumption increased 65% while consumption per capita increased 39% between 2000-2015 (Klein
292 et al., 2018). The excess or inappropriate use of antibiotics can lead to antibiotic resistance, as indicated by studies
293 showing an association between high use of antibiotics and enhanced antimicrobial resistance (AMR) (Chambers,
294 2001; Llor & Bjerrum, 2014). Wastewater has been used to monitor antibiotic presence and consumption patterns.
295 Zhang et al. measured loads of 23 antibiotics in wastewater from eight major WWTPs of Beijing (Zhang et al.,
296 2018). In another WBE study, antibiotic consumption was correlated with the flu season and the housing price
297 and population density of the catchment (Zhang et al., 2019). Another study in China assessed the use of six
298 antibiotics using WBE because there were no other data (Yuan, Liu, Huang, Yin, & Dang, 2016). In Milan, Italy,
299 antibiotic excretion was higher in winter than in summer, reflecting the higher rate of infections during winter
300 (Castiglioni et al., 2006). As antibiotic resistance genes emerge and spread globally, wastewater can monitor
301 sources of environmental antibiotic resistance. WBE can provide rapid information on community antibiotics
302 consumption in different time frames. A recent WBE study showed the power of analysing the consumption of
303 quinolones antibiotics and quinolones resistance genes in European wastewater. It found that higher daily load
304 qnrS gene were associated higher quinolone loads (Castrignano et al., 2020).

305 3.3. Relationship between socio-demographic catchment parameters and pharmaceutical use
306 The WBE approach allows the study of the relationships between consumption of chemicals and sociodemographic
307 features of catchment areas. This may extend the relevance of WBE in the social sciences to such fields as town
308 planning or local policy evaluation. These studies find predicted relationships between socioeconomic factors and
309 the consumption of legal and illegal compounds but they also uncovered novel relationships.

310 Changes in the socioeconomic composition of a population over time can be measured using WBE. In a 2016
311 Study, Thomaidis *et al*. analysed a suite of pharmaceuticals and drugs in the wastewater from Athens (Greece)
312 between 2010 and 2014, a period in which there was a severe economic downturn and the implementation of
313 austerity measures (Thomaidis et al., 2016). It showed staggering increases in the per capita consumption of
314 narcotic drugs such as methadone (7-fold) and psychiatric pharmaceuticals (35-fold), and antidepressants (11-
315 fold). By contrast, the consumption of amphetamine, antibiotics and NSAIDs decreased. This study demonstrates
316 how WBE can be used to document changes in drug consumption produced by large-scale socioeconomic
317 disruptions. Recently, Reinstadler et al. also showed the potential to investigate temporal changes during the
318 coronavirus disease 2019 (COVID-19) lockdown and quarantine in the catchment area of Innsbruck (Reinstadler
319 et al., 2021). This study showed that consumption of medicines prescribed for chronic pharmaceutical treatment

(e.g. oxazepam, carbamazepine, venlafaxine,etc.) remained unaffected by the public health crisis. Contrastingly, the consumption of pharmaceuticals for short-term use (e.g. acetaminophen, codeine and trimethoprim) declined during the COVID-19 pandemic, potentially as a result of improved population health or a reduction in the number of consultations of medical doctors or pharmacies.

Housing prices and density have been shown to be associated with the consumption of pharmaceuticals. A 2018 study measured 37 pharmaceuticals from eight WWTPs in Beijing (China), and related these to the average housing price and population density for each WWTP catchment (Zhang et al., 2018). These measures were highly correlated ($r = 0.92 – 0.93$) with the total load of pharmaceuticals. Because of the sampling strategy in this study (where one wastewater sample was deemed representative of a WWTP), these results may reflect increased pharmaceutical consumption by transient residents (i.e. commuting workers) rather than residents. Nevertheless, the results imply that higher economic status in China is linked to higher pharmaceutical use.

Relationships between WBE biomarkers and socioeconomic measures also include measures of demographics, education and more. An Australian study measured a suite of mostly drug and pharmaceutical biomarkers from wastewater samples collected at the same time as a national Census in 2019 (P. Choi et al., 2019). Per capita loads of opioids, antipsychotics and antidepressants were significantly higher in catchments with older, lower socioeconomic status populations. The loads of antibiotics cephlexin, sulfamethoxazole, and trimethoprim were not associated with either age or socioeconomics of the catchments. Strong correlations were found between specific drugs and socioeconomic measures. There were for example correlations between: tramadol use and the percentage of labourers in a population ($r = 0.84$), amitriptyline and a lack of high school education ($r = 0.77$), and there was an inverse relationship between pregabalin and high income ($r = -0.77$) in Australia (P. Choi et al., 2019). However, these associations may be influenced by the way reimbursement systems are set up. While WBE studies examining socioeconomics are unable to distinguish between correlation and causation, they can uncover important insights into how drug and other chemical consumption patterns are associated with socioeconomic characteristics.

A WBE study in Milan (Italy) found a significant correlation between airborne particulate matter and salbutamol (Fattore et al., 2016). This study clearly demonstrated the association between environmental changes (i.e. air pollution, pollen season) and higher consumption of a pharmaceutical to treat respiratory disease. This study demonstrates the potential of applying WBE to investigate environmental diseases. It provides a direct comparison

between pharmaceutical consumption and pollution levels at the same day, which can be used to investigate the relationship between environmental exposure and disease.

4. Future perspectives and developments

4.1. WBE as a promising complementary information source for DUR

The current review demonstrates ways in which WBE can potentially be utilised as a complementary tool in DUR but additional research is needed on methodological issues (i.e. in-sewer stability, pharmacokinetics, etc.) and data triangulation. Nonetheless we observe an increasing number of WBE applications on pharmaceuticals. Fig. 3 indicates where WBE could be applied as a complementary strategy to aid in filling the current knowledge gaps in the field of DUR and address the strengths of the different data sources. By triangulating data from the different pharmacoepidemiologic information sources, it may be possible to estimate the prevalence of use of pharmaceuticals more accurately. This information can be employed by policy-makers in the design and evaluation of pharmaceutical regulations.

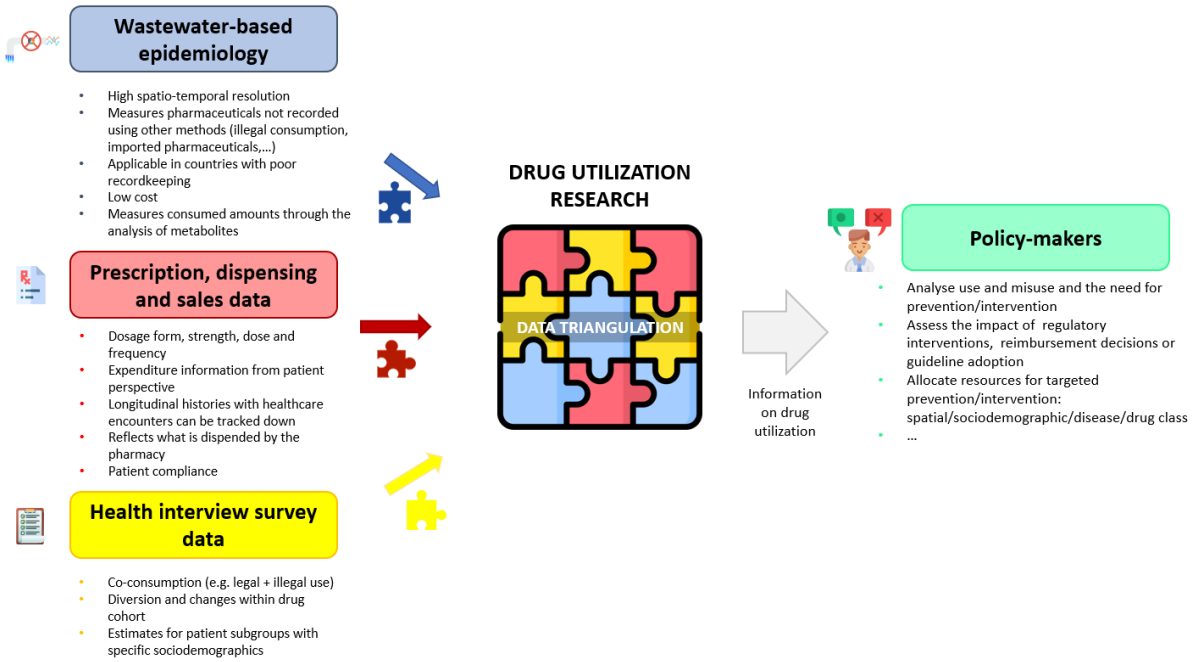


Fig. 3 The place of WBE in the myriad of pharmacoepidemiological information sources in the context of drug utilization research

A major advantage of WBE is that it may provide estimates of consumption for pharmaceuticals which are not recorded using other methods; either because they are consumed illegally, or that they are not recorded in existing data sets (e.g. the Pharmaceutical Benefit Scheme in Australia does not include private scripts or in-hospital use; some pharmaceuticals can be purchased without scripts) (Mellish et al., 2015). WBE can provide complementary

information on what proportion of pharmaceuticals that are sold, dispensed and/or prescribed are consumed by the population because it measures consumption through human metabolic excretion products in wastewater. Discrepancies between WBE and prescription data could indicate the degree of compliance to a medication regimen at a population scale. A pharmaceutical prescribed to a patient is not necessarily taken by the patient in prescribed amounts or the dispensed amounts (e.g. if some of the medicines are diverted to others).

Additionally, WBE may be a good alternative when prescription data are very difficult and sales data are too expensive. For countries with limited prescription and or sales data, WBE could provide cost effective measurements of the amounts of key compounds that are consumed. Additionally, many low income countries do not have a prescription system and allow many pharmaceuticals to be sold over the counter with poor record keeping (Borges, Chama, & Nilsson, 2016). WBE may be useful for surveillance of pharmaceutical regulation that are not captured through traditional datasets (e.g. for pharmaceuticals not subsidized or off-label indications not refunded by disability insurance). Some pharmaceuticals can also be obtained without prescription so their use will not be included in prescription data (e.g. online internet trades, import from neighbouring countries, over-the-counter sales, etc.).

The WBE approach can be especially helpful in monitoring the use of antibiotics (Zhang et al., 2019, 2018) and misuse of potentially addictive pharmaceuticals, such as opioids and benzodiazepines (Bade et al., 2020; Centazzo, Frederick, Jacox, Cheng, & Concheiro-Guisan, 2019; Croft et al., 2020; Duvallet, Hayes, Erickson, Chai, & Matus, 2020; Endo et al., 2020; Gushgari, Venkatesan, Chen, Steele, & Halden, 2019; Kim & Oh, 2020). Antibiotics are supplied in several countries without a prescription (e.g. previously prescribed courses, local markets or stores, diversion from families or friends) which facilitates the development and spread of antibiotic resistance (Bahta et al., 2020; Berendonk et al., 2015; Llor & Cots, 2009). A recent study by Castrignanò et al. found that higher total quinolone loads corresponded with a higher prevalence of quinolone resistance genes (measured through in-sewer investigation of *qnrS* genes) in the catchment areas (Castrignano et al., 2020). If estimated antibiotic DDDs in wastewater are substantially higher or lower than prescribed DDDs, the community may not be compliant with therapy. It might be difficult to accurately estimate compliance to antibiotic treatment at a population scale due to lack of knowledge of the optimal treatment length and varied treatment regimens for different infections. Nonetheless, it is worth investigating trends in the discrepancies between prescribed amounts of antibiotics and measured amounts in wastewater. Knowledge of total antibiotic loads is helpful to policy makers because of the strong quantitative link between antibiotic use and antibiotic resistance (World Health Organization (WHO), 2018). Another critical component of this aspect is that WBE can capture uses of pharmaceuticals in animal

husbandry if the runoff from such facilities is connected to the WWTP. This is obviously of high relevance for identifying inappropriate use of antibiotics leading to antimicrobial resistance as this is a global challenge with particularly poor data on antibiotic use in the general community (World Health Organization (WHO), 2015). Additionally, many non-antibiotic pharmaceuticals have shown ability to induce for antibiotic resistance (Berendonk et al., 2015; Singh et al., 2019).

4.2. Agreement between WBE data and other DUR information sources

Some efforts have already been done to triangulate WBE data with other DUR information sources. These WBE studies show reasonable relationships between WBE data on pharmaceuticals (e.g. oxazepam, atenolol, etc.) and prescription and sales data (Baker et al., 2014; Baz-Lomba et al., 2016; Been et al., 2015; Escolà Casas et al., 2021; He et al., 2020; Kasprzyk-Hordern et al., 2009; Rice, Kannan, Castrignanò, Jagadeesan, & Kasprzyk-Hordern, 2020; Riva et al., 2020; van Nuijs et al., 2015). For some pharmaceuticals (e.g. paracetamol, etc.), discrepancies were reported which may reflect over-the-counter pharmaceutical sales that are not included in prescription data (Baker et al., 2014; Crowley, White, Tscharke, & Gerber, 2017; van Nuijs et al., 2015). They could also reflect illegal sales of pharmaceuticals and import/export/diversion of pharmaceuticals to other geographical areas. Additionally, these differences may also arise from methodological uncertainties associated with WBE such as the direct disposal of parent compounds in the sewer, poor accuracy of excretion rates used in WBE's back-calculations and the complete/incomplete deconjugation of metabolites in the sewer (Escolà Casas et al., 2021). As indicated by van Nuijs et al, predicted loads and measured loads from the analysis of biomarkers in IWW could potentially not match accurately because WWTP catchment areas and postal codes do not correspond and not all households may be connected to the sewer system (van Nuijs et al., 2015). Prescribed pharmaceuticals may not be consumed by patients and the locality between the location of consumption and excretion might be different due to commuting.

Riva et al. used WBE with four prescription medicines intended for chronic use, including citalopram, enalapril, losartan and ramipril (Riva et al., 2020) in an attempt to assess compliance at a population level. WBE estimates and prescription data showed good agreement for citalopram, enalapril and their metabolites but in other cases there was a poor match. Although these discrepancies could be related to poor compliance or overuse, the authors acknowledged that the disagreement may also be the result of methodological uncertainties associated with each data source. In back-calculating daily defined doses they had to use potentially inaccurate excretion factors found in pharmacokinetic and metabolism studies. These correction factors are often obtained from clinical trials performed within a small subset of patients which may not be representative for the catchment population.

Additionally prescriptions may be incomplete in some areas (e.g. combination formulations only included in national figures but not in the regional database) and local prescription data may not match completely with the catchment area. Therefore, uncertainties in extrapolating to actual consumption should be adressed for each individual compound.

4.3. Early-warning system for pharmaceutical misuse

The illegal use of pharmaceuticals cannot be monitored using conventional datasets. Data triangulation can highlight potential discrepancies in the amounts used (e.g. identifying potential shifts to illicit use of pharmaceuticals) and potentially estimate the number of users, at a local and national level. In order to enable this comparison, it will be necessary to first monitor fluctuations in population-normalised mass loads of pharmaceuticals to understand trends in consumption patterns at a population level. The high temporal resolution of WBE enables researchers to monitor the evolution of the illicit market continuously, and with short-time lag. This may enable policy-makers to counter more swiftly the spread of counterfeit medicines and the recreational use of pharmaceuticals. It should be noted that while WBE can provide valuable information on the extent of counterfeit medication it cannot provide data on the composition (i.e. impurities, lack of API, dose of API, etc.) of counterfeit pharmaceuticals. WBE is not limited to measuring specific APIs; it can also be used to monitor their by-products or precursors in communities. In addition, the effects of legal import and export of pharmaceuticals (i.e. cheaper prices across national borders) cannot be excluded. These complications highlight the need for data triangulation to obtain a comprehensive view of total consumption and to identifying the extent in which pharmaceuticals are used appropriately.

In this light, Venhuis et al. highlighted the sale of sildenafil by online pharmacies in three Dutch communities (Venhuis et al., 2014). They compared estimates of sildenafil use based on WBE data with dispensing data on sildenafil that was legitimately sold. At least 60% of wastewater loads could not be explained by legal use of the drug. Causanilles et al. found also big discrepancies between WBE data and prescription data, if these were available (Causanilles et al., 2018) further documenting the power of WBE for documenting differences in local consumption patterns. However, a major limitation of this study is that prescription data was estimated by extrapolating the Dutch trend in prescription patterns, which might not be representative for other European countries.

Furthermore, historical WBE data could be used to quickly identify new consumption patterns at high spatio-temporal resolution early enough to avert an escalation in the use of pharmaceuticals. This approach can also be

used in specific locations to describe dissemination of a pattern of drug use of public health concern (e.g. increasing opioid consumption in rural areas in Australia).

4.4. Monitoring the effect of interventions and quality-control system in decision-making processes

In contrast to illicit drugs, tobacco and alcohol (Australian Crime Intelligence Commision, 2020; Mackie et al., 2019), WBE applications on pharmaceuticals have played a limited role in government strategies and decision-making. We propose several ways in which WBE may provide a complementary monitoring approach for governments and pharmaceutical policy makers.

The WBE approach provides a tool that can i) measure consumption of pharmaceuticals; ii) determine consumption patterns of pharmaceuticals at different spatial (e.g. local, regional, national, international) and temporal resolutions (e.g. daily, weekly, seasonally, yearly, etc.); and iii) by triangulating with other datasets, assess the impact that strategies or interventions have on consumption. These uses are not limited to a specific pharmaceutical, but could apply to a group of pharmaceuticals.

In this light, WBE may be particularly useful in monitoring the effect of an intervention or for assessing weekly or seasonal trends in pharmaceutical consumption. This could include an intervention such as a rescheduling or restricting of sale of a drug, a change in prescribing practice or regulations, or an education/advertising program to change the behaviours of presribers or individuals consuming pharmaceuticals. As yet, fewer studies have done so reported this, however one notable example is Zhang et al, which evaluated a potential decline in antibiotic use following interventions to prevent their prophylactic use during flu season in China (Zhang et al., 2019). One limitation of their study was the absence of samples from the period before the change occurred, which necessitated the use of other data sources. Partnerships between researchers and government agencies may assist in undertaking evaluations of policy changes before, during and after they occur. Additionally, WBE studies of pharmaceuticals are not necessarily limited in their choice of pharmaceuticals, as may be the case for surveys of drug use. If researchers/policy advisors are interested in the effects of an intervention directed at one pharmaceutical, WBE may be used to assess how this intervention has influenced consumption of another pharmaceutical. WBE could quickly measure changes in the consumption of pharmaceuticals during public health crises. In this light, WBE can be employed to investigate the impact of large-scale lifestyle disruptions such as the COVID-19 pandemic, continuously and with a shorter time lag than prescription or sales data (Been et al., 2021; Reinstadler et al., 2021).

Additionally, WBE can provide location specific information for DUR, which could be used to set area-based health care priorities for policy-makers. Areas with a higher burden of pharmaceutical misuse may require more

policy attention e.g. public or prescriber education, or the prevention of opioid overdose deaths by distributing naloxone sprays (Endo et al., 2020). WBE can identify areas with a higher burden of both legal and illegal opioid use. By prioritising problematic areas, decision-makers can respond to an evolving public health problems and address the social determinants of a public health crisis. The EMCDDA has already shown the effectiveness of this approach in addressing the consumption of illegal drugs in different European communities (European Monitoring Centre for Drugs and Drug Addiction, 2019a).

In the same manner, WBE is also able to evaluate the effects of the promotional activities of pharmaceutical companies, government or other institutions. This would enable policy-makers to assess if these approaches are an efficient use of resources. If the measures don't produce the desired effect, policy makers might look for different policies. WBE could be used, for example, to assess if statin compliance was adversely affected by exaggerated media reports about side effects (Nordestgaard, 2018).

Besides that, WBE can be used to quickly evaluate the effect of policy changes and to optimize prevention and harm reduction strategies targeting pharmaceuticals. Furthermore, by triangulating WBE data with other DUR data from different locations and information sources, decision-makers can identify and promote best practice. In this light, WBE can also be used to monitor and evaluate measures to ameliorate undesirable pharmaceutical use (e.g. over-use of antibiotics, benzodiazepines, Z-drugs, opioids etc.). This is especially helpful in situations where information on the consumption of pharmaceuticals needs to be obtained rapidly (e.g. socio-economic disruptions, health crises, epidemics, etc.). These interventions do not always have to be restricted to governments. Other organisations could potentially use WBE to assess the effects of their activities on the burden of pharmaceutical use (e.g. non-profit organisations that intervene to diminish addiction).

Furthermore, WBE can also provide an indicator of the extent of stockpiling of pharmaceuticals that have been removed from the market. WBE can complement DUR data source because sales and prescriptions of these pharmaceuticals are no longer available upon their removal from the market. It could also measure the extent of stockpiling after the sale and distribution of scheduled pharmaceuticals is prohibited. If these pharmaceuticals are still used in different communities, it would mean that they are acquired from other sources (e.g. online pharmacies, imported from other countries). WBE can also be applied to investigate if pharmaceutical reformulations (e.g. oxycodone reformulation in Australia to prevent injecting drug use) reduce consumption.

Two examples of governments that have used WBE for drug utilization research are the Australian National Wastewater Drug Monitoring Program (NWDMP) and the New Zealand National Wastewater Testing Programs.

These campaigns monitor an array of both illicit and licit drug metabolites (e.g. fentanyl and oxycodone) in a large proportion of the population. The Australian NWDMP demonstrated large spatial differences in per capita consumption of some pharmaceuticals such as fentanyl and oxycodone and that regional consumption for these was higher than in the capital cities, as well as changes in consumption over time (Australian Crime Intelligence Commision, 2020).

5. Methodological limitations

Despite the progress made through more than a decade of research, WBE has some intrinsic uncertainties related to sampling, biomarker stability, chemical analysis and real-time population that remain to be addressed (Castiglioni et al., 2013). Fig. 4 focuses on the different steps of WBE that should be checked when adopting this methodology. This flowchart also indicates the several sources of uncertainty associated with the different steps that need to be resolved when applying the WBE approach.

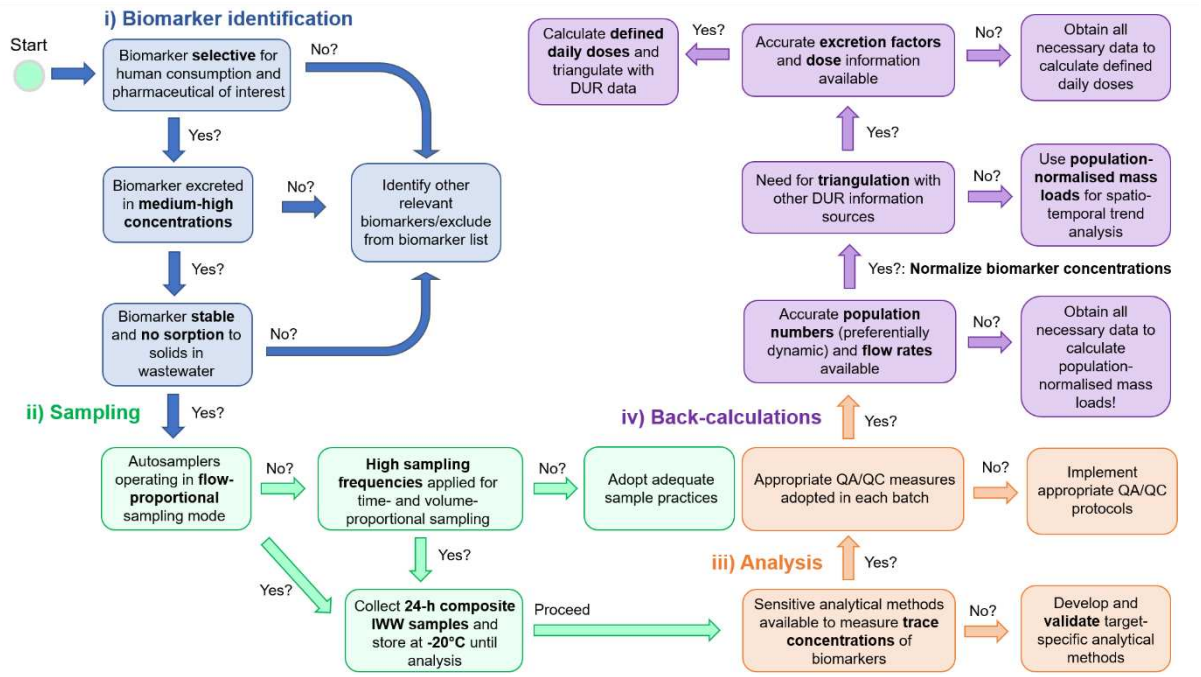


Fig. 4 Criteria for implementing the WBE approach

Efforts have been spent to evaluate these uncertainties and improve the accuracy of WBE estimations. In this sense, continuous flow-proportional sampling of the influent is recommended best practice for sampling (Ort, Lawrence, Reungoat, & Mueller, 2010), but in reality different sampling methods including time proportional or volume proportional sampling are used for logistical reasons. Most of the reported studies use fixed population numbers and it is difficult to verify if the fluctuations in population-normalized mass loads were due to variations in population size or changes in consumption patterns. Therefore, it would be more appropriate to use dynamic

population size numbers using either an anthropogenic biomarker or other data such as mobile phone data (Been et al., 2014; O'Brien et al., 2014; Thomas, Amador, Baz-Lomba, & Reid, 2017).

Metabolism and excretion of drugs are known to vary between individual or even within one individual under different health condition. Therefore, the excretion factor (EF), derived from these processes, contributes notably to the overall uncertainty of substance consumption estimation in WBE. EFs used in WBE applications are mostly derived from pharmacokinetic studies that had a limited number of participants and so may not reflect the average excretion profile in large populations (Kato, 1975; Klotz, 2011; Yasuda, Zhang, & Huang, 2008). Effort are being made to refine the EF of different drugs (Gracia-Lor, Zuccato, & Castiglioni, 2016). In recent years, some EF values derived from pharmacokinetics data were considered unsuitable for WBE application due to the large uncertainty involved. Therefore, estimation of absolute figures on back-calculated doses should be addressed more carefully. However, the primary focus of WBE has been to provide a complementary strategy to monitor spatial and temporal trends in consumption patterns of pharmaceuticals. For this purpose, a viable approach to uncertainty arising from EFs would be to use population-normalised mass loads and focus on the analysis of trends. Actually, back-calculating defined daily doses should only be considered when triangulation with other relevant DUR information sources is necessary. As an alternative, mass load of biomarkers in wastewater and prescription/sales statistics have been used to refine the EF for WBE applications. In some cases they have shown that these EFs can provide more accurate estimates of substance consumption in large populations (Thai, Lai, Bruno, et al., 2016).

Additional uncertainties can arise from the the non-use and/or direct disposal of unused drugs or the formation from other chemicals or conjugated drugs (Bettington et al., 2018; Guirguis, 2010). This is especially an issue if the parent drug is used as biomarker and if the unused drugs are disposed directly into the sewers (Petrie, Barden, & Kasprzyk-Hordern, 2015). Most pharmaceuticals possess chirality and racemic analysis can be used to distinguish between dumping and consumption of pharmaceuticals .

Stability of biomarkers is another source of uncertainties in WBE. Several studies have been carried out to understand degradation/fate processes and evaluate and model the in-sample and in-sewer biomarker stability in order to improve our understanding of the degree of this uncertainty (P. Choi et al., 2020; Gao et al., 2019; Li et al., 2019; Ramin et al., 2017). Using preservatives such as HCl and storing the samples at low temperature (preferably <-20 °C) are appropriate ways to minimise biomarker transformation. However, preservatives can only be introduced at the point of collection and so do not account for any in-sewer degradation. For in-sewer stability, the uncertainty could be much higher due to the lack of control over the microbiota present in the sewer system,

562 especially the sewer biofilms. Overall, higher biofilm area to bulk water volume ratio, higher wastewater
563 temperatures and longer hydraulic retention time promote biomarker transformation in the sewers (O'Brien et al.,
564 2017).

565 For some chemicals, sorption to particulate matter and/or biofilm can also contribute to the overall uncertainty of
566 the WBE approach, especially for biomarkers with high log Kow values such as methadone, fluoxetine and
567 atorvastatin (Baker & Kasprzyk-Hordern, 2011c; Ramin et al., 2017).

568 **6. Conclusion**

569 Influent wastewater contains a wealth of information on population health and lifestyle and can be considered as
570 a mirror of the society. The growing number of applications demonstrates how WBE can reduce current knowledge
571 gaps in DUR. In the future, DUR could benefit from a better understanding of pharmaceutical use in the general
572 population. In this light, WBE could provide information on pharmaceutical use not recorded using other methods
573 (e.g. illegal use, imported pharmaceuticals,…) and could be employed as an alternative in countries with poor
574 recordkeeping. Additionally, WBE has the potential to be used as an indicator on health aspects of populations
575 which can be obtained with fast turn-around-times at high spatial and temporal resolutions and therefore to be used
576 as early-warning system for more detailed investigations.However, knowledge of methodological issues and
577 compound-specific uncertainties (i.e. biomarker excretion, in-sewer stability, population catchment size) will be
578 needed to convert concentrations of human biomarkers to population-normalised loads and/or pharmaceutical
579 consumption.

580 We also clearly emphasize the importance of triangulating multiple sources of information (e.g.
581 prescription/sales/dispensing data, health interview survey data,…) to validate WBE measurements and obtain a
582 multi-angled view on the use of pharmaceuticals in different locations. Additionally, the high spatio-temporal
583 frequency of WBE enables correlation analysis to investigate association between pharmaceutical consumption
584 and socio-demographics in specific communities. This adaptable sampling frequency also enables the investigation
585 of the impact of interventions (e.g. pharmaceutical rescheduling, restricted sales, education initiatives…)
586 implemented by governmental agencies. It improves our understanding of pharmaceutical (mis)use for the
587 location-specific allocations of health care resources made by policy-makers. Finally, WBE is one of the few data
588 sources that can objectively measure the extent of illegal pharmaceutical consumption in the population. WBE and
589 other DUR information sources have their strength and weaknesses but the combination promises to be yield more
590 than the some of each.

Acknowledgements

None to declare

Declarations of conflicts of interest

We hereby declare that there are no conflicts of interest. This is an original study and the work has not been previously published as a whole or in part, and is not under consideration for publication elsewhere.

Funding information

Authors affiliated to the Toxicological Centre (University of Antwerp) were funded for this particular study by the European Union's Justice Programme—Drugs Policy Initiatives, EuSeME (project number 861602). The Queensland Alliance for Environmental Health Sciences (QAEHS), The University of Queensland gratefully acknowledges the financial support of the Queensland Department of Health. Jochen F. Mueller is funded by an ARC Australian Laureate Fellowship FL 200100028. This manuscript is partly funded by an Australian Research Council (ARC) Discovery project (DP180101475).

References

Ahmed, F., Tscharke, B., O'Brien, J., Thompson, J., Samanipour, S., Choi, P., … Thomas, K. (2020). Wastewater-based estimation of the prevalence of gout in Australia. *The Science of the Total Environment*, *715*, 136925. https://doi.org/10.1016/j.scitotenv.2020.136925

Andrés-Costa, M. J., Andreu, V., & Picó, Y. (2017). Liquid chromatography–mass spectrometry as a tool for wastewater-based epidemiology: Assessing new psychoactive substances and other human biomarkers. *TrAC Trends in Analytical Chemistry*, *94*, 21–38. https://doi.org/https://doi.org/10.1016/j.trac.2017.06.012

Australian Crime Intelligence Commision. (2020). *National Wastewater Drug Monitoring Program: Report 9*. Retrieved from https://www.acic.gov.au/sites/default/files/2020/03/nwdmp-r9-060220_ec_v8_small.pdf

Bade, R., Ghetia, M., White, J. M., & Gerber, C. (2020). Determination of prescribed and designer benzodiazepines and metabolites in influent wastewater. *Analytical Methods*, *12*(28), 3637–3644. https://doi.org/10.1039/D0AY00560F

Bahta, M., Tesfamariam, S., Weldemariam, D. G., Yemane, H., Tesfamariam, E. H., Alem, T., & Russom, M. (2020). Dispensing of antibiotics without prescription and associated factors in drug retail outlets of Eritrea: A simulated client method. *PloS One*, *15*(1), e0228013. https://doi.org/10.1371/journal.pone.0228013

Baker, D. R., Barron, L., & Kasprzyk-Hordern, B. (2014). Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part A: chemical analysis and drug use estimates. *The Science of the Total Environment*, *487*, 629–641. https://doi.org/10.1016/j.scitotenv.2013.11.107

Baker, D. R., & Kasprzyk-Hordern, B. (2011a). Critical evaluation of methodology commonly used in sample collection, storage and preparation for the analysis of pharmaceuticals and illicit drugs in surface water and wastewater by solid phase extraction and liquid chromatography-mass spectrometry. *Journal of Chromatography. A*, *1218*(44), 8036–8059. https://doi.org/10.1016/j.chroma.2011.09.012

Baker, D. R., & Kasprzyk-Hordern, B. (2011b). Multi-residue analysis of drugs of abuse in wastewater and surface water by solid-phase extraction and liquid chromatography–positive electrospray ionisation tandem mass spectrometry. *Journal of Chromatography A*, *1218*(12), 1620–1631. https://doi.org/https://doi.org/10.1016/j.chroma.2011.01.060

631 Baker, D. R., & Kasprzyk-Hordern, B. (2011c). Multi-residue determination of the sorption of illicit drugs and
632 pharmaceuticals to wastewater suspended particulate matter using pressurised liquid extraction, solid
633 phase extraction and liquid chromatography coupled with tandem mass spectrometry. *Journal of*
634 *Chromatography. A*, *1218*(44), 7901–7913. https://doi.org/10.1016/j.chroma.2011.08.092

635 Baker, D. R., Ocenaskova, V., Kvicalova, M., & Kasprzyk-Hordern, B. (2012). Drugs of abuse in wastewater
636 and suspended particulate matter--further developments in sewage epidemiology. *Environment*
637 *International*, *48*, 28–38. https://doi.org/10.1016/j.envint.2012.06.014

638 Banta-Green, C. J., Field, J. A., Chiaia, A. C., Sudakin, D. L., Power, L., & de Montigny, L. (2009). The spatial
639 epidemiology of cocaine, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) use: a
640 demonstration using a population measure of community drug load derived from municipal wastewater.
641 *Addiction (Abingdon, England)*, *104*(11), 1874–1880. https://doi.org/10.1111/j.1360-0443.2009.02678.x

642 Baz-Lomba, J. A., Salvatore, S., Gracia-Lor, E., Bade, R., Castiglioni, S., Castrignanò, E., … Thomas, K.
643 (2016). Comparison of pharmaceutical, illicit drug, alcohol, nicotine and caffeine levels in wastewater with
644 sale, seizure and consumption data for 8 European cities. *BMC Public Health*, *16*(1), 1035.
645 https://doi.org/10.1186/s12889-016-3686-5

646 Been, F., Benaglia, L., Lucia, S., Gervasoni, J.-P., Esseiva, P., & Delemont, O. (2015). Data triangulation in the
647 context of opioids monitoring via wastewater analyses. *Drug and Alcohol Dependence*, *151*, 203–210.
648 https://doi.org/10.1016/j.drugalcdep.2015.03.022

649 Been, F., Emke, E., Matias, J., Baz-Lomba, J. A., Boogaerts, T., Castiglioni, S., … Bijlsma, L. (2021). Changes
650 in drug use in European cities during early COVID-19 lockdowns – A snapshot from wastewater analysis.
651 *Environment International*, *153*, 106540. https://doi.org/https://doi.org/10.1016/j.envint.2021.106540

652 Been, F., Rossi, L., Ort, C., Rudaz, S., Delémont, O., & Esseiva, P. (2014). Population Normalization with
653 Ammonium in Wastewater-Based Epidemiology: Application to Illicit Drug Monitoring. *Environmental*
654 *Science & Technology*, *48*(14), 8162–8169. https://doi.org/10.1021/es5008388

655 Bérdy, J. (2012). Thoughts and facts about antibiotics: where we are now and where we are heading. *The*
656 *Journal of Antibiotics*, *65*(8), 385–395. https://doi.org/10.1038/ja.2012.27

657 Berendonk, T. U., Manaia, C. M., Merlin, C., Fatta-Kassinos, D., Cytryn, E., Walsh, F., … Martinez, J. L.
658 (2015). Tackling antibiotic resistance: the environmental framework. *Nature Reviews Microbiology*, *13*(5),

310–317. https://doi.org/10.1038/nrmicro3439

Bettington, E., Spinks, J., Kelly, F., Gallardo-Godoy, A., Nghiem, S., & Wheeler, A. J. (2018). When is a medicine unwanted, how is it disposed, and how might safe disposal be promoted? Insights from the Australian population. *Australian Health Review : A Publication of the Australian Hospital Association*, *42*(6), 709–717. https://doi.org/10.1071/ah16296

Bodik, I., Mackulak, T., Faberova, M., & Ivanova, L. (2016). Occurrence of illicit drugs and selected pharmaceuticals in Slovak municipal wastewater. *Environmental Science and Pollution Research International*, *23*(20), 21098–21105. https://doi.org/10.1007/s11356-016-7415-5

Boogaerts, T., Covaci, A., Kinyua, J., Neels, H., & van Nuijs, A. L. N. (2016). Spatial and temporal trends in alcohol consumption in Belgian cities: A wastewater-based approach. *Drug and Alcohol Dependence*, *160*, 170–176. https://doi.org/10.1016/j.drugalcdep.2016.01.002

Boogaerts, T., Degreef, M., Covaci, A., & van Nuijs, A. L. N. (2019). Development and validation of an analytical procedure to detect spatio-temporal differences in antidepressant use through a wastewater-based approach. *Talanta*, *200*, 340–349. https://doi.org/https://doi.org/10.1016/j.talanta.2019.03.052

Boogaerts, T., Quireyns, M., Covaci, A., De Loof, H., & van Nuijs, A. L. N. (2021). Analytical method for the simultaneous determination of a broad range of opioids in influent wastewater: Optimization, validation and applicability to monitor consumption patterns. *Talanta*, *232*, 122443. https://doi.org/https://doi.org/10.1016/j.talanta.2021.122443

Borges, L., Chama, T., & Nilsson, E. (2016). Primary data collection for drug utilization research. *Drug Utilization Research: Methods and Applications*, *29–38*, 31.

Botero-Coy, A. M., Martínez-Pachón, D., Boix, C., Rincón, R. J., Castillo, N., Arias-Marín, L. P., … Hernández, F. (2018). 'An investigation into the occurrence and removal of pharmaceuticals in Colombian wastewater.' *Science of The Total Environment*, *642*, 842–853. https://doi.org/https://doi.org/10.1016/j.scitotenv.2018.06.088

Burgard, D. A., Fuller, R., Becker, B., Ferrell, R., & Dinglasan-Panlilio, M. J. (2013). Potential trends in Attention Deficit Hyperactivity Disorder (ADHD) drug use on a college campus: wastewater analysis of amphetamine and ritalinic acid. *The Science of the Total Environment*, *450–451*, 242–249. https://doi.org/10.1016/j.scitotenv.2013.02.020

687 Burgard, D. A., Williams, J., Westerman, D., Rushing, R., Carpenter, R., LaRock, A., … Banta-Green, C. J.
688 (2019). Using wastewater-based analysis to monitor the effects of legalized retail sales on cannabis
689 consumption in Washington State, USA. *Addiction (Abingdon, England)*, *114*(9), 1582–1590.
690 https://doi.org/10.1111/add.14641

691 Castiglioni, S., Bagnati, R., Fanelli, R., Pomati, F., Calamari, D., & Zuccato, E. (2006). Removal of
692 pharmaceuticals in sewage treatment plants in Italy. *Environmental Science & Technology*, *40*(1), 357–
693 363. https://doi.org/10.1021/es050991m

694 Castiglioni, S., Bijlsma, L., Covaci, A., Emke, E., Hernández, F., Reid, M., … Zuccato, E. (2013). Evaluation of
695 uncertainties associated with the determination of community drug use through the measurement of
696 sewage drug biomarkers. *Environmental Science & Technology*, *47*(3), 1452–1460.
697 https://doi.org/10.1021/es302722f

698 Castrignano, E., Yang, Z., Feil, E. J., Bade, R., Castiglioni, S., Causanilles, A., … Kasprzyk-Hordern, B. (2020).
699 Enantiomeric profiling of quinolones and quinolones resistance gene qnrS in European wastewaters. *Water*
700 *Research*, *175*, 115653. https://doi.org/10.1016/j.watres.2020.115653

701 Causanilles, A., Emke, E., & de Voogt, P. (2016). Determination of phosphodiesterase type V inhibitors in
702 wastewater by direct injection followed by liquid chromatography coupled to tandem mass spectrometry.
703 *The Science of the Total Environment*, *565*, 140–147. https://doi.org/10.1016/j.scitotenv.2016.04.158

704 Causanilles, A., Rojas Cantillano, D., Emke, E., Bade, R., Baz-Lomba, J. A., Castiglioni, S., … de Voogt, P.
705 (2018). Comparison of phosphodiesterase type V inhibitors use in eight European cities through analysis
706 of urban wastewater. *Environment International*, *115*, 279–284.
707 https://doi.org/10.1016/j.envint.2018.03.039

708 Causanilles, A., Ruepert, C., Ibanez, M., Emke, E., Hernandez, F., & de Voogt, P. (2017). Occurrence and fate
709 of illicit drugs and pharmaceuticals in wastewater from two wastewater treatment plants in Costa Rica. *The*
710 *Science of the Total Environment*, *599–600*, 98–107. https://doi.org/10.1016/j.scitotenv.2017.04.202

711 Centazzo, N., Frederick, B.-M., Jacox, A., Cheng, S.-Y., & Concheiro-Guisan, M. (2019). Wastewater analysis
712 for nicotine, cocaine, amphetamines, opioids and cannabis in New York City. *Forensic Sciences Research*,
713 *4*(2), 152–167. https://doi.org/10.1080/20961790.2019.1609388

714 Chambers, H. F. (2001). The changing epidemiology of Staphylococcus aureus? *Emerging Infectious Diseases*,

715 *7*(2), 178–182. https://doi.org/10.3201/eid0702.010204

716 Chen, Y., & Briesacher, B. A. (2011). Use of instrumental variable in prescription drug research with
717 observational data: a systematic review. *Journal of Clinical Epidemiology*, *64*(6), 687–700.
718 https://doi.org/10.1016/j.jclinepi.2010.09.006

719 Choi, P., Li, J., Gao, J., O'Brien, J. W., Thomas, K. V., Thai, P. K., … Mueller, J. F. (2020). Considerations for
720 assessing stability of wastewater-based epidemiology biomarkers using biofilm-free and sewer reactor
721 tests. *Science of The Total Environment*, *709*, 136228.
722 https://doi.org/https://doi.org/10.1016/j.scitotenv.2019.136228

723 Choi, P. M., O'Brien, J. W., Li, J., Jiang, G., Thomas, K. V, & Mueller, J. F. (2018). Population histamine
724 burden assessed using wastewater-based epidemiology: The association of 1,4methylimidazole acetic acid
725 and fexofenadine. *Environment International*, *120*, 172–180. https://doi.org/10.1016/j.envint.2018.08.009

726 Choi, P., Tscharke, B. J., Donner, E., O'Brien, J. W., Grant, S. C., Kaserzon, S. L., … Mueller, J. F. (2018).
727 Wastewater-based epidemiology biomarkers: Past, present and future. *TrAC Trends in Analytical*
728 *Chemistry*, *105*, 453–469. https://doi.org/https://doi.org/10.1016/j.trac.2018.06.004

729 Choi, P., Tscharke, B., Samanipour, S., Hall, W. D., Gartner, C. E., Mueller, J. F., … O'Brien, J. W. (2019).
730 Social, demographic, and economic correlates of food and chemical consumption measured by
731 wastewater-based epidemiology. *Proceedings of the National Academy of Sciences of the United States of*
732 *America*, *116*(43), 21864–21873. https://doi.org/10.1073/pnas.1910242116

733 Croft, T. L., Huffines, R. A., Pathak, M., & Subedi, B. (2020). Prevalence of illicit and prescribed
734 neuropsychiatric drugs in three communities in Kentucky using wastewater-based epidemiology and
735 Monte Carlo simulation for the estimation of associated uncertainties. *Journal of Hazardous Materials*,
736 *384*, 121306. https://doi.org/https://doi.org/10.1016/j.jhazmat.2019.121306

737 Crowley, P., White, J. M., Tscharke, B. J., & Gerber, C. (2017, July). Wastewater analysis shows a large
738 decrease in oxycodone use in Adelaide. *The Medical Journal of Australia*. Australia.
739 https://doi.org/10.5694/mja17.00137

740 Daughton, C. G. (2018). Monitoring wastewater for assessing community health: Sewage Chemical-Information
741 Mining (SCIM). *The Science of the Total Environment*, *619–620*, 748–764.
742 https://doi.org/10.1016/j.scitotenv.2017.11.102

743 Diamanti, K., Aalizadeh, R., Alygizakis, N., Galani, A., Mardal, M., & Thomaidis, N. S. (2019). Wide-scope
744 target and suspect screening methodologies to investigate the occurrence of new psychoactive substances
745 in influent wastewater from Athens. *The Science of the Total Environment*, *685*, 1058–1065.
746 https://doi.org/10.1016/j.scitotenv.2019.06.173

747 Duan, Y.-P., Meng, X.-Z., Wen, Z.-H., & Chen, L. (2013). Acidic pharmaceuticals in domestic wastewater and
748 receiving water from hyper-urbanization city of China (Shanghai): environmental release and ecological
749 risk. *Environmental Science and Pollution Research International*, *20*(1), 108–116.
750 https://doi.org/10.1007/s11356-012-1000-3

751 Duvallet, C., Hayes, B. D., Erickson, T. B., Chai, P. R., & Matus, M. (2020). Mapping Community Opioid
752 Exposure Through Wastewater-Based Epidemiology as a Means to Engage Pharmacies in Harm Reduction
753 Efforts. *Preventing Chronic Disease*, *17*, E91. https://doi.org/10.5888/pcd17.200053

754 Endo, N., Ghaeli, N., Duvallet, C., Foppe, K., Erickson, T. B., Matus, M., & Chai, P. R. (2020). Rapid
755 Assessment of Opioid Exposure and Treatment in Cities Through Robotic Collection and Chemical
756 Analysis of Wastewater. *Journal of Medical Toxicology : Official Journal of the American College of*
757 *Medical Toxicology*, *16*(2), 195–203. https://doi.org/10.1007/s13181-019-00756-5

758 Escolà Casas, M., Schröter, N. S., Zammit, I., Castaño-Trias, M., Rodriguez-Mozaz, S., Gago-Ferrero, P., &
759 Corominas, L. (2021). Showcasing the potential of wastewater-based epidemiology to track
760 pharmaceuticals consumption in cities: Comparison against prescription data collected at fine spatial
761 resolution. *Environment International*, *150*, 106404.
762 https://doi.org/https://doi.org/10.1016/j.envint.2021.106404

763 European Monitoring Centre for Drugs and Drug Addiction. (2019a). *European Drug Report 2019: Trends and*
764 *developments*. Lisbon.

765 European Monitoring Centre for Drugs and Drug Addiction. (2019b). Policy and practice briefings: Addressing
766 the misuse of medicines. Retrieved from http://www.emcdda.europa.eu/best-practice/briefings/addressing-
767 misuse-medicines_en

768 Fáberová, M., Bodík, I., Ivanová, L., Grabic, R., & Mackuľak, T. (2017). Frequency and use of pharmaceuticals
769 in selected Slovakian town via wastewater analysis. *Monatshefte Für Chemie - Chemical Monthly*, *148*(3),
770 441–448. https://doi.org/10.1007/s00706-016-1853-0

771 Fallati, L., Castiglioni, S., Galli, P., Riva, F., Gracia-Lor, E., Gonzalez-Marino, I., … Zuccato, E. (2020). Use of
772 legal and illegal substances in Male (Republic of Maldives) assessed by wastewater analysis. *The Science*
773 *of the Total Environment*, *698*, 134207. https://doi.org/10.1016/j.scitotenv.2019.134207

774 Fatta, D., Achilleos, A., Nikolaou, A., & Meriç, S. (2007). Analytical methods for tracing pharmaceutical
775 residues in water and wastewater. *TrAC Trends in Analytical Chemistry*, *26*(6), 515–533.
776 https://doi.org/https://doi.org/10.1016/j.trac.2007.02.001

777 Fattore, E., Davoli, E., Castiglioni, S., Bosetti, C., Re Depaolini, A., Marzona, I., … Fanelli, R. (2016).
778 Wastewater-based epidemiological evaluation of the effect of air pollution on short-acting beta-agonist
779 consumption for acute asthma treatment. *Environmental Research*, *150*, 106–111.
780 https://doi.org/10.1016/j.envres.2016.05.051

781 Gao, J., Li, J., Jiang, G., Shypanski, A. H., Nieradzik, L. M., Yuan, Z., … Thai, P. K. (2019). Systematic
782 evaluation of biomarker stability in pilot scale sewer pipes. *Water Research*, *151*, 447–455.
783 https://doi.org/10.1016/j.watres.2018.12.032

784 Gao, J., O'Brien, J., Du, P., Li, X., Ort, C., Mueller, J. F., & Thai, P. K. (2016). Measuring selected PPCPs in
785 wastewater to estimate the population in different cities in China. *The Science of the Total Environment*,
786 *568*, 164–170. https://doi.org/10.1016/j.scitotenv.2016.05.216

787 Golovko, O., Kumar, V., Fedorova, G., Randak, T., & Grabic, R. (2014). Seasonal changes in antibiotics,
788 antidepressants/psychiatric drugs, antihistamines and lipid regulators in a wastewater treatment plant.
789 *Chemosphere*, *111*, 418–426. https://doi.org/10.1016/j.chemosphere.2014.03.132

790 Gomez-Canela, C., Sala-Comorera, T., Pueyo, V., Barata, C., & Lacorte, S. (2019). Analysis of 44
791 pharmaceuticals consumed by elderly using liquid chromatography coupled to tandem mass spectrometry.
792 *Journal of Pharmaceutical and Biomedical Analysis*, *168*, 55–63.
793 https://doi.org/10.1016/j.jpba.2019.02.016

794 Gong, L., Goswami, S., Giacomini, K. M., Altman, R. B., & Klein, T. E. (2012). Metformin pathways:
795 pharmacokinetics and pharmacodynamics. *Pharmacogenetics and Genomics*, *22*(11), 820–827.
796 https://doi.org/10.1097/FPC.0b013e3283559b22

797 Gracia-Lor, E., Castiglioni, S., Bade, R., Been, F., Castrignano, E., Covaci, A., … Bijlsma, L. (2017). Measuring
798 biomarkers in wastewater as a new source of epidemiological information: Current state and future

perspectives. *Environment International*, *99*, 131–150. https://doi.org/10.1016/j.envint.2016.12.016

Gracia-Lor, E., Zuccato, E., & Castiglioni, S. (2016). Refining correction factors for back-calculation of illicit drug use. *The Science of the Total Environment*, *573*, 1648–1659. https://doi.org/10.1016/j.scitotenv.2016.09.179

Guirguis, K. (2010). Medications collected for disposal by outreach pharmacists in Australia. *Pharmacy World & Science : PWS*, *32*(1), 52–58. https://doi.org/10.1007/s11096-009-9340-x

Gul, W., Gul, S. W., Stamper, B., Godfrey, M., & ElSohly, M. A. (2018). LC-MS-MS Method Development and Analysis of Stimulants, Opiates, Synthetic Opiates, PCP, and Benzodiazepines in Wastewater. Preponderance of these Drugs During Football Games. *Methods in Molecular Biology (Clifton, N.J.)*, *1810*, 149–182. https://doi.org/10.1007/978-1-4939-8579-1_15

Gul, W., Stamper, B., Godfrey, M., Gul, S. W., & ElSohly, M. A. (2016). LC-MS-MS Method for Analysis of Opiates in Wastewater During Football Games II. *Journal of Analytical Toxicology*, *40*(5), 330–337. https://doi.org/10.1093/jat/bkw022

Gushgari, A. J., Driver, E. M., Steele, J. C., & Halden, R. U. (2018). Tracking narcotics consumption at a Southwestern U.S. university campus by wastewater-based epidemiology. *Journal of Hazardous Materials*, *359*, 437–444. https://doi.org/10.1016/j.jhazmat.2018.07.073

Gushgari, A. J., Venkatesan, A. K., Chen, J., Steele, J. C., & Halden, R. U. (2019). Long-term tracking of opioid consumption in two United States cities using wastewater-based epidemiology approach. *Water Research*, *161*, 171–180. https://doi.org/https://doi.org/10.1016/j.watres.2019.06.003

Hanefeld, M. (2014). Use of insulin in type 2 diabetes: what we learned from recent clinical trials on the benefits of early insulin initiation. *Diabetes & Metabolism*, *40*(6), 391–399. https://doi.org/10.1016/j.diabet.2014.08.006

He, K., Borthwick, A. G., Lin, Y., Li, Y., Fu, J., Wong, Y., & Liu, W. (2020). Sale-based estimation of pharmaceutical concentrations and associated environmental risk in the Japanese wastewater system. *Environment International*, *139*, 105690. https://doi.org/10.1016/j.envint.2020.105690

Huerta-Fontela, M., Galceran, M. T., Martin-Alonso, J., & Ventura, F. (2008). Occurrence of psychoactive stimulatory drugs in wastewaters in north-eastern Spain. *Science of The Total Environment*, *397*(1), 31–40.

https://doi.org/https://doi.org/10.1016/j.scitotenv.2008.02.057

Karolak, S., Nefau, T., Bailly, E., Solgadi, A., & Levi, Y. (2010). Estimation of illicit drugs consumption by wastewater analysis in Paris area (France). *Forensic Science International*, *200*(1), 153–160. https://doi.org/https://doi.org/10.1016/j.forsciint.2010.04.007

Kasprzyk-Hordern, B., Dinsdale, R. M., & Guwy, A. J. (2009). Illicit drugs and pharmaceuticals in the environment – Forensic applications of environmental data. Part 1: Estimation of the usage of drugs in local communities. *Environmental Pollution*, *157*(6), 1773–1777. https://doi.org/https://doi.org/10.1016/j.envpol.2009.03.017

Kato, R. (1975). Sex-Related Differences in Drug Metabolism. *Drug Metabolism Reviews*, *3*(1), 1–32. https://doi.org/10.3109/03602537408993737

Kim, K. Y., & Oh, J.-E. (2020). Evaluation of pharmaceutical abuse and illicit drug use in South Korea by wastewater-based epidemiology. *Journal of Hazardous Materials*, *396*, 122622. https://doi.org/https://doi.org/10.1016/j.jhazmat.2020.122622

Klein, E. Y., Van Boeckel, T. P., Martinez, E. M., Pant, S., Gandra, S., Levin, S. A., … Laxminarayan, R. (2018). Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences*, *115*(15), E3463 LP-E3470. https://doi.org/10.1073/pnas.1717295115

Klotz, S. S. and U. (2011). Age-Related Changes in Pharmacokinetics. *Current Drug Metabolism*. https://doi.org/http://dx.doi.org/10.2174/138920011796504527

Kosma, C. I., Nannou, C. I., Boti, V. I., & Albanis, T. A. (2019). Psychiatrics and selected metabolites in hospital and urban wastewaters: Occurrence, removal, mass loading, seasonal influence and risk assessment. *The Science of the Total Environment*, *659*, 1473–1483. https://doi.org/10.1016/j.scitotenv.2018.12.421

Krizman-Matasic, I., Senta, I., Kostanjevecki, P., Ahel, M., & Terzic, S. (2019). Long-term monitoring of drug consumption patterns in a large-sized European city using wastewater-based epidemiology: Comparison of two sampling schemes for the assessment of multiannual trends. *The Science of the Total Environment*, *647*, 474–485. https://doi.org/10.1016/j.scitotenv.2018.07.441

Krizman, I., Senta, I., Ahel, M., & Terzic, S. (2016). Wastewater-based assessment of regional and temporal consumption patterns of illicit drugs and therapeutic opioids in Croatia. *The Science of the Total Environment*, *566–567*, 454–462. https://doi.org/10.1016/j.scitotenv.2016.05.075

Lai, F. Y., Bruno, R., Hall, W., Gartner, C., Ort, C., Kirkbride, P., … Mueller, J. F. (2013). Profiles of illicit drug use during annual key holiday and control periods in Australia: wastewater analysis in an urban, a semi-rural and a vacation area. *Addiction (Abingdon, England)*, *108*(3), 556–565. https://doi.org/10.1111/add.12006

Lai, F. Y., Ort, C., Gartner, C., Carter, S., Prichard, J., Kirkbride, P., … Mueller, J. F. (2011). Refining the estimation of illicit drug consumptions from wastewater analysis: Co-analysis of prescription pharmaceuticals and uncertainty assessment. *Water Research*, *45*(15), 4437–4448. https://doi.org/https://doi.org/10.1016/j.watres.2011.05.042

Li, J., Gao, J., Thai, P. K., Shypanski, A., Nieradzik, L., Mueller, J. F., … Jiang, G. (2019). Experimental Investigation and Modeling of the Transformation of Illicit Drugs in a Pilot-Scale Sewer System. *Environmental Science & Technology*, *53*(8), 4556–4565. https://doi.org/10.1021/acs.est.8b06169

Lichtenberg, F. R. (2014). Pharmaceutical innovation and longevity growth in 30 developing and high-income countries, 2000–2009. *Health Policy and Technology*, *3*(1), 36–58. https://doi.org/https://doi.org/10.1016/j.hlpt.2013.09.005

Llor, C., & Bjerrum, L. (2014). Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Therapeutic Advances in Drug Safety*, *5*(6), 229–241. https://doi.org/10.1177/2042098614554919

Llor, C., & Cots, J. M. (2009). The Sale of Antibiotics without Prescription in Pharmacies in Catalonia, Spain. *Clinical Infectious Diseases*, *48*(10), 1345–1349. https://doi.org/10.1086/598183

Mackie, R. S., Tscharke, B. J., O'Brien, J. W., Choi, P. M., Gartner, C. E., Thomas, K. V, & Mueller, J. F. (2019). Trends in nicotine consumption between 2010 and 2017 in an Australian city using the wastewater-based epidemiology approach. *Environment International*, *125*, 184–190. https://doi.org/10.1016/j.envint.2019.01.053

Mackulak, T., Birosova, L., Gal, M., Bodik, I., Grabic, R., Ryba, J., & Skubak, J. (2016). Wastewater analysis: the mean of the monitoring of frequently prescribed pharmaceuticals in Slovakia. *Environmental*

881 *Monitoring and Assessment*, *188*(1), 18. https://doi.org/10.1007/s10661-015-5011-7

882 Mackulak, T., Brandeburova, P., Grencikova, A., Bodik, I., Stanova, A. V., Golovko, O., … Grabic, R. (2019).
883 Music festivals and drugs: Wastewater analysis. *The Science of the Total Environment*, *659*, 326–334.
884 https://doi.org/10.1016/j.scitotenv.2018.12.275

885 Mari, F., Politi, L., Biggeri, A., Accetta, G., Trignano, C., Di Padua, M., & Bertol, E. (2009). Cocaine and heroin
886 in waste water plants: A 1-year study in the city of Florence, Italy. *Forensic Science International*, *189*(1),
887 88–92. https://doi.org/https://doi.org/10.1016/j.forsciint.2009.04.018

888 Mastroianni, N., Lopez-Garcia, E., Postigo, C., Barcelo, D., & Lopez de Alda, M. (2017). Five-year monitoring
889 of 19 illicit and legal substances of abuse at the inlet of a wastewater treatment plant in Barcelona (NE
890 Spain) and estimation of drug consumption patterns and trends. *The Science of the Total Environment*, *609*,
891 916–926. https://doi.org/10.1016/j.scitotenv.2017.07.126

892 Mellish, L., Karanges, E. A., Litchfield, M. J., Schaffer, A. L., Blanch, B., Daniels, B. J., … Pearson, S.-A.
893 (2015). The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers.
894 *BMC Research Notes*, *8*, 634. https://doi.org/10.1186/s13104-015-1616-8

895 Metcalfe, C., Tindale, K., Li, H., Rodayan, A., & Yargeau, V. (2010). Illicit drugs in Canadian municipal
896 wastewater and estimates of community drug use. *Environmental Pollution*, *158*(10), 3179–3185.
897 https://doi.org/https://doi.org/10.1016/j.envpol.2010.07.002

898 Mirzaei, R., Mesdaghinia, A., Hoseini, S. S., & Yunesian, M. (2019). Antibiotics in urban wastewater and rivers
899 of Tehran, Iran: Consumption, mass load, occurrence, and ecological risk. *Chemosphere*, *221*, 55–66.
900 https://doi.org/10.1016/j.chemosphere.2018.12.187

901 National Institute of Drug Abuse. (2018). Misuse of Prescription Drugs. Retrieved from
902 https://www.drugabuse.gov/publications/misuse-prescription-drugs/overview

903 Nordestgaard, B. G. (2018). Why do the Media report negative news about statins? *European Heart Journal*,
904 *39*(5), 337–338. https://doi.org/10.1093/eurheartj/ehx789

905 O'Brien, J. W., Banks, A. P. W., Novic, A. J., Mueller, J. F., Jiang, G., Ort, C., … Thai, P. K. (2017). Impact of
906 in-Sewer Degradation of Pharmaceutical and Personal Care Products (PPCPs) Population Markers on a
907 Population Model. *Environmental Science & Technology*, *51*(7), 3816–3823.

https://doi.org/10.1021/acs.est.6b02755

O'Brien, J. W., Thai, P. K., Eaglesham, G., Ort, C., Scheidegger, A., Carter, S., … Mueller, J. F. (2014). A Model to Estimate the Population Contributing to the Wastewater Using Samples Collected on Census Day. *Environmental Science & Technology*, *48*(1), 517–525. https://doi.org/10.1021/es403251g

Organisation for Economic Co-operation and Development. (2018). *Health at Glance: Europe 2018*.

Ort, C., Lawrence, M. G., Reungoat, J., Eaglesham, G., Carter, S., & Keller, J. (2010). Determining the fraction of pharmaceutical residues in wastewater originating from a hospital. *Water Research*, *44*(2), 605–615. https://doi.org/10.1016/j.watres.2009.08.002

Ort, C., Lawrence, M. G., Reungoat, J., & Mueller, J. F. (2010). Sampling for PPCPs in Wastewater Systems: Comparison of Different Sampling Modes and Optimization Strategies. *Environmental Science & Technology*, *44*(16), 6289–6296. https://doi.org/10.1021/es100778d

Ostman, M., Fick, J., Nasstrom, E., & Lindberg, R. H. (2014). A snapshot of illicit drug use in Sweden acquired through sewage water analysis. *The Science of the Total Environment*, *472*, 862–871. https://doi.org/10.1016/j.scitotenv.2013.11.081

Papageorgiou, M., Kosma, C., & Lambropoulou, D. (2016). Seasonal occurrence, removal, mass loading and environmental risk assessment of 55 pharmaceuticals and personal care products in a municipal wastewater treatment plant in Central Greece. *The Science of the Total Environment*, *543*(Pt A), 547–569. https://doi.org/10.1016/j.scitotenv.2015.11.047

Pereira, A. M. P. T., Silva, L. J. G., Meisel, L. M., Lino, C. M., & Pena, A. (2015). Environmental impact of pharmaceuticals from Portuguese wastewaters: geographical and seasonal occurrence, removal and risk assessment. *Environmental Research*, *136*, 108–119. https://doi.org/10.1016/j.envres.2014.09.041

Petrie, B., Barden, R., & Kasprzyk-Hordern, B. (2015). A review on emerging contaminants in wastewaters and the environment: Current knowledge, understudied areas and recommendations for future monitoring. *Water Research*, *72*, 3–27. https://doi.org/https://doi.org/10.1016/j.watres.2014.08.053

Phung, D., Mueller, J., Lai, F. Y., O'Brien, J., Dang, N., Morawska, L., & Thai, P. K. (2017). Can wastewater-based epidemiology be used to evaluate the health impact of temperature? – An exploratory study in an Australian population. *Environmental Research*, *156*, 113–119.

https://doi.org/https://doi.org/10.1016/j.envres.2017.03.023

Poluzzi, E., Krska, J., Godman, B., Vander Stichele, R., Vlahović-Palčevski, V., Taxis, K., … Andersen, M. (2016). *Drug utilization research. methods and applications.* Chichester, Wiley Blackwell 2016. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,url,uid&db=cat01187a&AN=ABC.c.lvd.14401147&lang=nl&site=eds-live

Postigo, C., López de Alda, M. J., & Barceló, D. (2010). Drugs of abuse and their metabolites in the Ebro River basin: Occurrence in sewage and surface water, sewage treatment plants removal efficiency, and collective drug usage estimation. *Environment International*, *36*(1), 75–84. https://doi.org/https://doi.org/10.1016/j.envint.2009.10.004

Proudman, C., Lester, S. E., Gonzalez-Chica, D. A., Gill, T. K., Dalbeth, N., & Hill, C. L. (2019). Gout, flares, and allopurinol use: a population-based study. *Arthritis Research & Therapy*, *21*(1), 132. https://doi.org/10.1186/s13075-019-1918-7

Ramin, P., Brock, A. L., Causanilles, A., Valverde-Pérez, B., Emke, E., de Voogt, P., … Plósz, B. G. (2017). Transformation and Sorption of Illicit Drug Biomarkers in Sewer Biofilms. *Environmental Science & Technology*, *51*(18), 10572–10584. https://doi.org/10.1021/acs.est.6b06277

Reinstadler, V., Ausweger, V., Grabher, A.-L., Kreidl, M., Huber, S., Grander, J., … Oberacher, H. (2021). Monitoring drug consumption in Innsbruck during coronavirus disease 2019 (COVID-19) lockdown by wastewater analysis. *Science of The Total Environment*, *757*, 144006. https://doi.org/https://doi.org/10.1016/j.scitotenv.2020.144006

Rice, J., Kannan, A. M., Castrignanò, E., Jagadeesan, K., & Kasprzyk-Hordern, B. (2020). Wastewater-based epidemiology combined with local prescription analysis as a tool for temporalmonitoring of drugs trends - A UK perspective. *Science of The Total Environment*, *735*, 139433. https://doi.org/https://doi.org/10.1016/j.scitotenv.2020.139433

Riva, F., Castiglioni, S., Pacciani, C., & Zuccato, E. (2020). Testing urban wastewater to assess compliance with prescription data through wastewater-based epidemiology: First case study in Italy. *The Science of the Total Environment*, *739*, 139741. https://doi.org/10.1016/j.scitotenv.2020.139741

Robinson, P. C., Kempe, S., Tebbutt, I., & Roberts, L. (2017). Epidemiology of inpatient gout in Australia and

New Zealand: temporal trends, comorbidities and gout flare site. *International Journal of Rheumatic Diseases*, *20*(6), 779–784. https://doi.org/10.1111/1756-185X.12941

Scheurer, M., Brauch, H.-J., & Lange, F. T. (2009). Analysis and occurrence of seven artificial sweeteners in German waste water and surface water and in soil aquifer treatment (SAT). *Analytical and Bioanalytical Chemistry*, *394*(6), 1585–1594. https://doi.org/10.1007/s00216-009-2881-y

Shao, X.-T., Cong, Z.-X., Liu, S.-Y., Wang, Z., Zheng, X.-Y., & Wang, D.-G. (2021). Spatial analysis of metformin use compared with nicotine and caffeine consumption through wastewater-based epidemiology in China. *Ecotoxicology and Environmental Safety*, *208*, 111623. https://doi.org/10.1016/j.ecoenv.2020.111623

SHELDON, J., ANDERSON, J., & STONER, L. (1965). SERUM CONCENTRATION AND URINARY EXCRETION OF ORAL SULFONYLUREA COMPOUNDS: RELATION TO DIABETIC CONTROL. *Diabetes*, *14*, 362–367. https://doi.org/10.2337/diab.14.6.362

Silva, L., Miguel, E. De, Peiteado, D., Villalba, A., Mola, M., Pinto, J., & Ventura, F. S. (2010). Compliance in gout patients. *Acta Reumatologica Portuguesa*, *35*(5), 466–474.

Singh, T., Singh, P. K., Dar, S. A., Haque, S., Akhter, N., & Das, S. (2019). Changing paradigm of antibiotic resistance amongst Escherichia coli isolates in Indian pediatric population. *PloS One*, *14*(4), e0213850–e0213850. https://doi.org/10.1371/journal.pone.0213850

Skees, A. J., Foppe, K. S., Loganathan, B., & Subedi, B. (2018). Contamination profiles, mass loadings, and sewage epidemiology of neuropsychiatric and illicit drugs in wastewater and river waters from a community in the Midwestern United States. *The Science of the Total Environment*, *631–632*, 1457–1464. https://doi.org/10.1016/j.scitotenv.2018.03.060

Song, X.-B., Shao, X.-T., Liu, S.-Y., Tan, D.-Q., Wang, Z., & Wang, D.-G. (2020). Assessment of metformin, nicotine, caffeine, and methamphetamine use during Chinese public holidays. *Chemosphere*, *258*, 127354. https://doi.org/https://doi.org/10.1016/j.chemosphere.2020.127354

Stamper, B., Gul, W., Godfrey, M., Gul, S. W., & ElSohly, M. A. (2016). LC-MS-MS Method for the Analysis of Miscellaneous Drugs in Wastewater During Football Games III. *Journal of Analytical Toxicology*, *40*(8), 694–699. https://doi.org/10.1093/jat/bkw081

990 Subedi, B., Balakrishna, K., Joshua, D. I., & Kannan, K. (2017). Mass loading and removal of pharmaceuticals
991 and personal care products including psychoactives, antihypertensives, and antibiotics in two sewage
992 treatment plants in southern India. *Chemosphere*, *167*, 429–437.
993 https://doi.org/10.1016/j.chemosphere.2016.10.026

994 Subedi, B., & Kannan, K. (2015). Occurrence and fate of select psychoactive pharmaceuticals and
995 antihypertensives in two wastewater treatment plants in New York State, USA. *The Science of the Total*
996 *Environment*, *514*, 273–280. https://doi.org/10.1016/j.scitotenv.2015.01.098

997 Terzic, S., Senta, I., & Ahel, M. (2010). Illicit drugs in wastewater of the city of Zagreb (Croatia) – Estimation of
998 drug abuse in a transition country. *Environmental Pollution*, *158*(8), 2686–2693.
999 https://doi.org/https://doi.org/10.1016/j.envpol.2010.04.020

1000 Thai, P. K., Lai, F. Y., Bruno, R., van Dyken, E., Hall, W., O'Brien, J., … Mueller, J. F. (2016). Refining the
1001 excretion factors of methadone and codeine for wastewater analysis - Combining data from
1002 pharmacokinetic and wastewater studies. *Environment International*, *94*, 307–314.
1003 https://doi.org/10.1016/j.envint.2016.05.033

1004 Thai, P. K., Lai, F. Y., Edirisinghe, M., Hall, W., Bruno, R., O'Brien, J. W., … Mueller, J. F. (2016). Monitoring
1005 temporal changes in use of two cathinones in a large urban catchment in Queensland, Australia. *Science of*
1006 *The Total Environment*, *545–546*, 250–255. https://doi.org/https://doi.org/10.1016/j.scitotenv.2015.12.038

1007 Thiebault, T., Fougere, L., Destandau, E., Rety, M., & Jacob, J. (2017). Temporal dynamics of human-excreted
1008 pollutants in wastewater treatment plant influents: Toward a better knowledge of mass load fluctuations.
1009 *The Science of the Total Environment*, *596–597*, 246–255. https://doi.org/10.1016/j.scitotenv.2017.04.130

1010 Thomaidis, N. S., Gago-Ferrero, P., Ort, C., Maragou, N. C., Alygizakis, N. A., Borova, V. L., & Dasenaki, M.
1011 E. (2016). Reflection of Socioeconomic Changes in Wastewater: Licit and Illicit Drug Use Patterns.
1012 *Environmental Science & Technology*, *50*(18), 10065–10072. https://doi.org/10.1021/acs.est.6b02417

1013 Thomas, K. V, Amador, A., Baz-Lomba, J. A., & Reid, M. (2017). Use of Mobile Device Data To Better
1014 Estimate Dynamic Population Size for Wastewater-Based Epidemiology. *Environmental Science &*
1015 *Technology*, *51*(19), 11363–11370. https://doi.org/10.1021/acs.est.7b02538

1016 Thomas, K. V, & Reid, M. J. (2011). What Else Can the Analysis of Sewage for Urinary Biomarkers Reveal
1017 About Communities? *Environmental Science & Technology*, *45*(18), 7611–7612.

https://doi.org/10.1021/es202522d

Tscharke, B. J., Chen, C., Gerber, J. P., & White, J. M. (2015). Trends in stimulant use in Australia: A comparison of wastewater analysis and population surveys. *The Science of the Total Environment*, *536*, 331–337. https://doi.org/10.1016/j.scitotenv.2015.07.078

Tscharke, B. J., Chen, C., Gerber, J. P., & White, J. M. (2016). Temporal trends in drug use in Adelaide, South Australia by wastewater analysis. *The Science of the Total Environment*, *565*, 384–391. https://doi.org/10.1016/j.scitotenv.2016.04.183

van Dyken, E., Lai, F. Y., Thai, P. K., Ort, C., Bruno, R., Hall, W., … Prichard, J. (2016). Challenges and opportunities in using wastewater analysis to measure drug use in a small prison facility. *Drug and Alcohol Review*, *35*(2), 138–147. https://doi.org/10.1111/dar.12156

van Nuijs, A. L. N., Castiglioni, S., Tarcomnicu, I., Postigo, C., de Alda, M. L., Neels, H., … Covaci, A. (2011). Illicit drug consumption estimations derived from wastewater analysis: A critical review. *Science of The Total Environment*, *409*(19), 3564–3577. https://doi.org/https://doi.org/10.1016/j.scitotenv.2010.05.030

van Nuijs, A. L. N., Covaci, A., Beyers, H., Bervoets, L., Blust, R., Verpooten, G., … Jorens, P. G. (2015). Do concentrations of pharmaceuticals in sewage reflect prescription figures? *Environmental Science and Pollution Research International*, *22*(12), 9110–9118. https://doi.org/10.1007/s11356-014-4066-2

van Nuijs, A. L. N., Pecceu, B., Theunis, L., Dubois, N., Charlier, C., Jorens, P. G., … Covaci, A. (2009). Can cocaine use be evaluated through analysis of wastewater? A nation-wide approach conducted in Belgium. *Addiction (Abingdon, England)*, *104*(5), 734–741. https://doi.org/10.1111/j.1360-0443.2009.02523.x

van Wel, J. H. P., Gracia-Lor, E., van Nuijs, A. L. N., Kinyua, J., Salvatore, S., Castiglioni, S., … Van Hal, G. (2016). Investigation of agreement between wastewater-based epidemiology and survey data on alcohol and nicotine use in a community. *Drug and Alcohol Dependence*, *162*, 170–175. https://doi.org/10.1016/j.drugalcdep.2016.03.002

Venhuis, B. J., de Voogt, P., Emke, E., Causanilles, A., & Keizers, P. H. J. (2014, July). Success of rogue online pharmacies: sewage study of sildenafil in the Netherlands. *BMJ (Clinical Research Ed.)*. England. https://doi.org/10.1136/bmj.g4317

World Health Organization. (2003). *Introduction to Drug Utilization Research*. Oslo.

World Health Organization (WHO). (2015). *GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE*. Retrieved from https://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/

World Health Organization (WHO). (2018). Wide differences in antibiotic use between countries, according to new data from WHO. Retrieved from https://www.who.int/medicines/areas/rational_use/oms-amr-amc-report-2016-2018-media-note/en/

Xiao, Y., Shao, X.-T., Tan, D.-Q., Yan, J.-H., Pei, W., Wang, Z., … Wang, D.-G. (2019). Assessing the trend of diabetes mellitus by analyzing metformin as a biomarker in wastewater. *The Science of the Total Environment*, *688*, 281–287. https://doi.org/10.1016/j.scitotenv.2019.06.117

Yan, J.-H., Xiao, Y., Tan, D.-Q., Shao, X.-T., Wang, Z., & Wang, D.-G. (2019). Wastewater analysis reveals spatial pattern in consumption of anti-diabetes drug metformin in China. *Chemosphere*, *222*, 688–695. https://doi.org/10.1016/j.chemosphere.2019.01.151

Yan, Q., Gao, X., Huang, L., Gan, X.-M., Zhang, Y.-X., Chen, Y.-P., … Guo, J.-S. (2014). Occurrence and fate of pharmaceutically active compounds in the largest municipal wastewater treatment plant in Southwest China: mass balance analysis and consumption back-calculated model. *Chemosphere*, *99*, 160–170. https://doi.org/10.1016/j.chemosphere.2013.10.062

Yargeau, V., Taylor, B., Li, H., Rodayan, A., & Metcalfe, C. D. (2014). Analysis of drugs of abuse in wastewater from two Canadian cities. *The Science of the Total Environment*, *487*, 722–730. https://doi.org/10.1016/j.scitotenv.2013.11.094

Yasuda, S. U., Zhang, L., & Huang, S.-M. (2008). The Role of Ethnicity in Variability in Response to Drugs: Focus on Clinical Pharmacology Studies. *Clinical Pharmacology & Therapeutics*, *84*(3), 417–423. https://doi.org/10.1038/clpt.2008.141

Yuan, S.-F., Liu, Z.-H., Huang, R.-P., Yin, H., & Dang, Z. (2016). Levels of six antibiotics used in China estimated by means of wastewater-based epidemiology. *Water Science and Technology : A Journal of the International Association on Water Pollution Research*, *73*(4), 769–775. https://doi.org/10.2166/wst.2015.526

Zhang, Y., Duan, L., Wang, B., Du, Y., Cagnetta, G., Huang, J., … Yu, G. (2019). Wastewater-based epidemiology in Beijing, China: Prevalence of antibiotic use in flu season and association of pharmaceuticals and personal care products with socioeconomic characteristics. *Environment*

International, *125*, 152–160. https://doi.org/10.1016/j.envint.2019.01.061

Zhang, Y., Wang, B., Cagnetta, G., Duan, L., Yang, J., Deng, S., … Yu, G. (2018). Typical pharmaceuticals in major WWTPs in Beijing, China: Occurrence, load pattern and calculation reliability. *Water Research*, *140*, 291–300. https://doi.org/10.1016/j.watres.2018.04.056

Zuccato, E., Chiabrando, C., Castiglioni, S., Bagnati, R., & Fanelli, R. (2008). Estimating community drug abuse by wastewater analysis. *Environmental Health Perspectives*, *116*(8), 1027–1032. https://doi.org/10.1289/ehp.11022

Zuccato, E., Chiabrando, C., Castiglioni, S., Calamari, D., Bagnati, R., Schiarea, S., & Fanelli, R. (2005). Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse. *Environmental Health : A Global Access Science Source*, *4*, 14. https://doi.org/10.1186/1476-069X-4-14